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A METHOD FOR THE ESTIMATION OF THE ACTUAL NUMBER OF TUBERCLE BACILLI IN TUBERCULOUS SPUTUM.

WITH A NOTE ON THE GENERAL APPLICATION OF THE METHOD TO BACTERIOLOGY.[1]

By George H. F. Nuttall, M. D., Ph. D. (Göttingen.)

(*From the Pathological Laboratory of the Johns Hopkins University*).

The statement frequently made of late, that the number of tubercle bacilli is often largely increased in the sputum of phthisical patients undergoing the Koch treatment, led the writer to make some observations in this direction.

If one only stops to think over the methods heretofore in vogue for determining simply the relative number of tubercle bacilli in sputum, one cannot but be struck by their extreme crudeness if not absurdity.

The first observations made with a view to determine the variation in the number of bacilli in sputum, for as yet no estimates of their *actual* numbers have been made, were those of Gaffky[4] in 1883, and, as his method has come down in clinical practice almost unaltered, it may be advisable for the sake of completeness to briefly review it.

Gaffky examined the sputum of 14 cases by making cover-glass smear-preparations in the ordinary manner and staining them by the Ehrlich method. Each day he prepared but one cover-glass from the sputum of each case. Depending upon the number of bacilli found on the cover-glasses he classified the latter into ten divisions.

According to this, "Condition 1" includes cover-glasses which when examined are found to contain 1-4 bacilli. "Condition 10" on the other hand shows an "enormous quantity in each field." *The numbers of bacilli in most cases he considered as impossible to even approximately calculate and he had to remain content with subjective estimates.* The following represents this classification of Gaffky's.

Condition	1.	On the whole cover-glass					1–4 bacilli.
"	2.	On several fields an average of					1 bacillus.
"	3.	On one field	"	"	"		1 "
"	4.	"	"	"	"	"	2–3 bacilli.
"	5.	"	"	"	"	"	4–6 "
"	6.	"	"	"	"	"	7–12 "
"	7.	"	"	"	"	"	rather many.
"	8.	"	"	"	"	"	many.
"	9.	"	"	"	"	"	very many.
"	10.	"	"	"	"	"	enormous quantity.

Upon the method of making smear-preparations such as Gaffky and others have used, it is scarcely necessary to dwell as it is the method generally in vogue. The varying thickness of the layer of sputum thus applied to the cover-glass must give erroneous impressions of the numbers of bacilli. One great source of error lies in the direction to seek samples from particular portions of the sputum where experience has taught observers that bacilli are most likely to be found. *Even if one does not pick out such a "likely place" the very unequal distribution of the bacilli in un-*

[1] Reported to the Johns Hopkins Hospital Medical Society, Baltimore, April 6th, 1891.

altered sputum renders any attempt at a count of little or no value. The whole value of the old method lies in diagnosis, and even here if there are few bacilli present, methods presently to be described must be resorted to.

The first thing that is necessary, if one wishes to form a correct idea as to the relative or actual number of bacilli in a specimen of sputum, is to distribute the bacilli evenly in suspension through the latter. To do this the whole nature of sputum must be altered, the muco-purulent masses broken up, the viscidity overcome—then, and then only can comparable results be obtained.

It is curious that no observations having any value in this direction have as yet been made. Previous observers have added caustic potash or borax to sputum with a view to making a homogeneous mixture and letting the bacilli gravitate to the bottom of the vessel. The idea here was to increase the chances of finding bacilli when so few were in the sputum that the ordinary methods of investigation might show none.

In the enormous literature on tuberculosis one finds very little that can be said to bear on our problem.

Biedert[2] in 1886 described a method which seems only recently to have come into general notice—the object of the method being to find bacilli when few are present in a quantity of sputum. He added two per cent. caustic potash solution to sputum and after boiling the mixture placed it in a conical glass and allowed sedimentation to occur. On decanting the supernatant fluid bacilli otherwise difficult or impossible to find were readily discovered in the deposit at the bottom of the vessel. In a recent article he again dwells on the value of the method.

Philip[8] (1886) recommends in cases where one has difficulty in finding the bacilli in sputum, or where much cellular or slimy matter is present, that one place the sputum for 12 to 24 hours in the thermostat, protecting it against evaporation and dust. Even thick "balled" sputum will thus separate into two layers, an under layer made up of cell elements and slime, and an upper fluid layer which is rich in bacilli—the latter he considers to have multiplied. On this question of whether the tubercle bacilli multiply in sputum or not, I have made some observations which will be presently given; suffice it to say that Philip's method of observing the sputum was totally inadequate to determine the matter.

Stroschein[10] (1889) advised for quantitative (?) estimates of tubercle bacilli in sputum, that one take from 5 to 10 cc. of the sputum to be examined and shake it up with one, two or three times its volume of a mixture (in the proportion of 1:3) of borax, boracic-acid and water. After shaking for a minute and the larger flocculi have disappeared, he pours the sputum mixture into a conical glass and allows sedimentation to occur. After 24 to 58 hours the clear supernatant fluid is decanted off and the sediment at the bottom examined for bacilli.

Kühne[6] (1890) dwells on the importance at present laid on estimates of the number of bacilli in sputum, and considers that as yet no good method has been found. To overcome the viscidity of the sputum and obtain a thin even layer on a cover-glass he used concentrated aqueous borax solution, adding the same in as much as an equal volume to the sputum; the latter thus prepared remains good for weeks, putrefaction being prevented, and the tubercle bacilli continuing to stain well. For sputa not possessing a high degree of viscidity he found concentrated aqueous solution of carbonate of ammonia to act very well, the salt evaporating partly on heating and being easily dissolved in acids.

More recently Mühlhäuser[7] has written on the Biedert method, which he considers he has simplified and improved. He does not advise the use of stronger solutions of caustic potash than 2 per cent. He takes only from 1–3 g. of sputum instead of the larger quantity taken by Biedert, and adds thereto from 6–8 times the volume of caustic potash solution.

Stone[9] has lately made some observations with the view of verifying the statement that the tubercle bacilli multiply in sputum which has been kept standing at the ordinary room temperature. He allowed tuberculous sputum to stand in a number of jars for about three months, examining it for bacilli before and after it had stood that length of time. The increase observed, Stone is inclined to ascribe on the whole, simply "to the increased density of the sputum, caused by evaporation, and to possible carelessness in the selection of parts for the first examination." The two sources of error which he mentions in the quoted words are very grave; the mere fact that there was a "selection of parts" at the first observation condemns the experiment, and the evaporation should certainly have been guarded against.

Immerwahr[5] has just reported the examination by him of the sputum of 109 cases of tuberculosis undergoing the Koch treatment. He classified the sputa according to the Gaffky table although he says in connection with this method: "It can happen that of two equally practiced observers the one will find many, the other few bacilli in one and the same specimen of sputum." When few bacilli were present he used the Biedert sedimentation method—the latter, he states, not affecting the staining of the bacilli. He stained the bacilli by the Gabbet method.

The following detailed description of the method employed by the writer to determine the actual number of tubercle bacilli in tuberculous sputum will, he fears, give the reader the impression that the method is difficult and complicated. The method is really simple in practice.

METHOD.

Preparation of the Sputum.

The total amount of sputum expectorated during every 24 hours was caught in covered, scrupulously clean, conical glasses and measured therein. The proportion of muco-purulent matter to the fluid part was noted in each case, as also the general appearances of the sputum. Depending upon the degree of viscidity and numbers of bacilli present in the sputum, a varying amount of 5 per cent. caustic potash solution was added to it (from ½ to an equal volume), and after the caustic potash had had the desired effect of rendering the sputum perfectly fluid, more or less water was added to dilute the mixture. The sputum having been measured in the conical glass, (which had the advantage of allowing the muco-purulent matter to float in a layer at the top so that it could be approximately measured,) was poured into a perfectly clean wide-mouthed bottle containing fine (sterilized) gravel or broken glass. The conical glass was then rinsed out and cleaned of any still adhering sputum by means of a measured amount of the caustic potash solution, which in turn was added to the sputum in the bottle. The latter, closed by a rubber stopper, was then transferred to a shaking machine,[1] where it was vigorously shaken for five minutes and then allowed to stand until the caustic potash

[1] The shaking machine used in these experiments, popularly known as a "milk punch shake" was found to be most efficient. It is manufactured by Whitall, Tatum & Co., Philadelphia, and is inexpensive—the machine is called the "Silent."

had had time to act. Very viscid sputum was then warmed at body temperature. As soon as the caustic potash had rendered the sputum homogeneous a measured quantity of water, usually an equal volume, or less (preferably distilled), was added and the mixture again shaken. The sputum thus treated was of pale green or yellowish-brown color, and contained only small fragments of elastic tissue where the latter was present. The sputum having stood 2–4 hours, was again shaken for 5–10 minutes, and was then ready for the next operation.

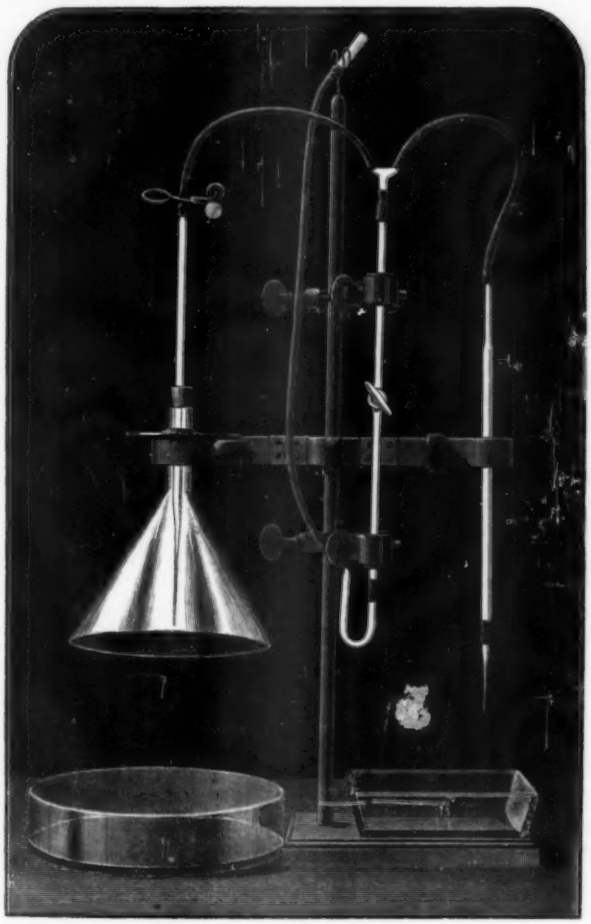

FIG. 1.

The Dropping Apparatus.

Though there are physical difficulties in the way of obtaining a succession of drops of absolutely uniform size, the difference is too minute to have any appreciable influence on our calculations, as a number of control experiments will presently show. The writer has found the simple apparatus represented in the accompanying illustration to be most effectual. It consists of a finely graduated burette, to which a finely drawn out dropper is attached by a rubber coupling. From the upper end of the burette proceeds a piece of rubber tubing which leads—a glass stop-cock intervening—to a mouth-piece which can be placed at the highest point of the apparatus out of danger of any possible contamination. Sterilized mouth-pieces in test-tubes were always kept on hand. (The object of the inverted funnel on the opposite side of the burette is described in the note at the end of the article; it has no bearing here.)

The glass stop-cock is of ordinary pattern, being only modified to suit the conditions in the following manner. The writer found it impossible by means of clamps on rubber tubing, or filling the stop-cock aperture with paraffin, through which a pinhole ran, to obtain a useful dropper. He might have resorted to more complicated apparatus, but simplicity being desirable he preferred not to. By simply filing a small groove (see fig. 2) with a triangular file on one side of the aperture in the stop-cock, the groove gradually fading as it proceeds away from the opening, a most effective and simple means of controlling the rate of dropping was found. In a fraction of a minute the desired rate of flow could be obtained, the size of the minute capillary opening being perfectly regulatable and the regularity of the dropping remarkable. Under the dropper a glass dish was placed, in which and over which all the manipulation occurred.

FIG. 2.

The sputum having been removed from the shaking machine, was immediately (or after an interval of two or three minutes) drawn up into the burette and the rate of dropping properly regulated.

Catching, Spreading and Drying the Drops, and Surrounding them with a Black Ring.

To one side of the dropper, along a low ledge, a number of perfectly clean, as yet unused, cover-glasses are placed with their edges projecting and all turned the same way. The drops are counted as they fall at regular intervals out of a given cubic centimeter or half centimeter of the burette—a number of those counted being caught as nearly as possible on the centre of each cover-glass. Any appreciable variation in the rate of flow and the size of the drops which the changing height of the column of fluid might give is thus corrected.

If you are working with a suspension of organisms in pure distilled water, you can allow the drop to dry in situ, but this will not do for sputum, as the latter forms too thick a film on drying unless it is spread out; the objections to a thick film being that it is prone to detach itself from the cover-glass, that it is difficult or impossible to properly decolorize, and that it is also extremely fatiguing to examine microscopically, owing to the constant focussing that is necessary. In practice it has been found that the smallest drops are the most satisfactory to work with as they give the thinnest films when spread in the manner about to be described. The best size obtained was when the drops were falling at the rate of 100 to 150 to the cubic centimeter.

It being necessary then to spread the drops of sputum, this was found to be accomplished best and most uniformly by using a turn-table, which was kept running smoothly but slowly by a small motor—the drops being spread by a very fine platinum needle, the extreme end of which was bent at about an angle of 45°. The platinum needle, from the fact that it removes a certain amount of fluid from the drop, introduces an error into the calculations—this error, however, is very small and practically constant. The needle enables one to spread the drops over a large surface and to do so uniformly; the contour of the spread drop is moreover perfectly circular, as one can see by observing the concentric circular guide-lines engraved on the plate of the turn-table.

From the turn-table the spread drops are immediately transferred to a brass plate, which is maintained in a horizontal position by a levelling tripod, and is warmed to 35–40° C., but not more, the object of the heating being merely to facilitate the drying of the drops. The latter dry rapidly, forming a large number of delicate concentric rings, reminding one of the microscopic picture presented by starch grains. If the plate is not quite horizontal the last point of the drop to dry may lie excentrically, but the drying will usually be perfectly concentric if one guards against unequal heating of the plate, currents of air and any deviation of the plate from the horizontal. The drops having dried, are returned to the turn-table, and after being carefully centred, are closely surrounded with a delicate ring of a paint composed of lamp-black mixed with serum, applied with a very small camel's hair brush.[1] The object of the lampblack ring will be presently described. When a drop did not dry quite concentrically, black lines running outward from the ring indicated the direction of the excentricity.

Covering the dried Sputum-drops with a Film of Serum.

The next step is to return the drop to the warm plate and by means of a spray[2] apply a delicate film of serum over it—the film being best applied by letting the first minute droplets dry, then spraying with sufficient rapidity to let the last droplets run together to form the film. The sterilized fluid serum used, was diluted usually with one-half its volume of sterilized distilled water, as one must guard against too thick a film on account of the difficulty there is in decolorizing it. A little practice soon shows one how to apply a perfect film, there being danger of being too hasty in not letting the first sprayings dry and as a result washing bacilli over the boundary formed by the lamp-black ring.

By raising the temperature of the plate to 80° or 90° C, one now coagulates the serum film.

One can now proceed to stain the drops or do what I did in these experiments—that is, extract the caustic potash from the drops through the film by means of alcohol which can be heated in a thermostat to the proper degree to increase its solvent action. The drops may be kept soaking, if desired, for several days in small glass vessels with tightly fitting covers to insure against evaporation. After removal from the alcohol the cover-glasses are allowed to dry on filter-paper and are then placed in small envelopes on which one notes the number of the observation. When the caustic potash is not removed there is a tendency for it to draw in water from the staining media or decolorizing solutions, and as a result the film balloons and not infrequently bursts—which phenomenon gives one the satisfaction at any rate of knowing that *one has really succeeded by means of the spray in applying a perfect enclosing membrane which will allow none of the bacilli in the dried drop of sputum to escape* or be washed away whilst we proceed to stain and mount. What is more we have applied a film without disturbing the bacilli on the cover-glass.

The Staining.

The best staining was obtained by using Ziehl-Neelsen carbol-fuchsin warmed in a watch-glass until it steamed—the cover-glasses being allowed to float drop-side down on the stain for a sufficient period (5–10 minutes) and being moved around on the surface of the stain with a needle. Although this stain is very tenacious only freshly colored specimens were examined.

The Decolorizer.

Recent observers have objected to the use of the usual solutions of mineral acids employed for decolorization on the ground that they decolorize many tubercle bacilli completely and as a result give a very wrong idea of the actual number present. I had a similar experience and feared for a time that my observations would come to a standstill on account of this difficulty. Kühne's suggestion to use fluoresceïn instead of the strong acid solutions usually in vogue, was followed by better results, but I found that by carefully using very dilute sulphuric acid and alcohol alternately, I obtained a better result even than with fluoresceïn.[1]

On removing the cover-glass from the stain, it was washed usually in three alcohols and then dipped into a solution composed of 150 parts water, 50 parts alcohol and 20–30 drops pure sulphuric acid. The specimen was then washed in water, and if necessary returned to the alcohol or acid again; in this way the drop and film were very gradually and carefully decolorized, the other bacteria contained in the sputum often forming a delicate background, on which only the very evenly distributed brightly stained tubercle bacilli appeared, all other cellular elements having disappeared, owing to the solvent action of the caustic potash. The bacilli can now be counted with ease.

The small drops decolorize almost if not quite uniformly from the margin to the centre—the result being that one has apparently only a pale pink film on the cover-glass, the film being a little more colored within the lampblack ring. Owing to the drop having dried in a very thin layer, the bacilli contained therein are all, or nearly all, on the same plane; the result is that one needs to do but little focussing, as the object is moved under the objective.

After a thorough washing in water the stained preparations were dried by gentle pressure between two pieces of filter paper or by draining from the margin. They were thus without the application of any heat after staining, mounted in balsam—the line on the cover-glass indicating the asymmetry in the drop being placed at right angles to the length of the slide.

The Object of the Lamp-black Ring.

The lamp-black ring includes all the area covered by the bacilli and being on exactly the same plane with them aids one in rapidly bringing the microscope to a focus. I have acquired the habit of always focussing on this lamp-black ring, and have found it to

[1] Almost by accident it was found that lamp-black mixed with serum and water formed an excellent black paint very suitable for the purpose One simply rubs the constituents together with a large stiff brush in a cup, and when the paint dries, all one has to do is to add a little water and rub it up afresh. One is able to paint very delicate rings with this paint on clean glass surfaces and to fix them by coagulation. It also forms a beautiful dull black on wood or metal and does not rub off on the finger if applied properly. This paint will answer perfectly for blackening any parts of optical instruments; the writer can recommend its use very highly.

[2] For this purpose an ordinary metal spray such as is used for perfume was employed. It must be one of those where the tube conducting the air from the bulb throws a jet across the orifice of the tube which leads into the fluid. The ordinary hard rubber spray did not do, as it frequently sputtered and many of the droplets contained bubbles of air.

[1] The difference between the decolorizing agents used is made strikingly evident by this method. The ordinary strong (25 per cent.) solutions of sulphuric acid left only 12,000 bacilli stained in drops which when decolorized with fluoresceïn showed upwards of 50,000. On the other hand a drop decolorized with fluoresceïn showed 154,592 when the dilute acid such as I used showed 202,180. In another case the fluoresceïn left 187,307 bacilli stained, the dilute acid 207,340, conclusively showing the superiority of the latter agent in point of delicacy.

remove a good deal of the strain on the eyes which is felt in focussing on colorless or barely stained surfaces. The ring also saves one unnecessary searching for bacilli beyond the margin of the drop, which is also a strain taken off one's eyes when the drop contains but few bacilli. I might casually remark that this ring has been found very useful in examining drop cultures.

THE MICROSCOPE.

The microscope used in these experiments was a large Zeiss stand, with a 1-12th apochromatic homogeneous-immersion objective and eye-piece, No. 12. A mechanical stage was used and the following modifications introduced:

FIG. 3.

The Eye-piece (see fig. 3). A square diaphragm traversed on one side of the centre by a hair-line was placed in the eye-piece with a view to cutting off the outer portions of the ordinary circular field which are necessarily not in sharp focus when the centre is. This considerably lessens one's chances of omitting to count any bacilli, the effort of counting the latter at the margin of a circular field, combined with the constant focussing that is necessary, being after a while quite unbearable. If one has a square diaphragm and a thinly spread drop, the focussing has scarcely to be altered, as the mechanical stage moves the object under the observer's eye. The bacilli were counted as they passed under the hair-line. It was found to be less fatiguing to have the apparent motion of the objects always toward the observer—that is, from above downward, when the microscope was tilted.

The Field Indicator (see fig. 4). Owing to the coarseness of the divisions on the mechanical stage, it was necessary to construct an apparatus of the form illustrated. One cannot accurately move the slide the width of a field by simply looking through the microscope when one has to do so very frequently—one is apt to let the fields observed overlap each other, and if no objects appear on a given area, one is apt to quite lose one's bearings. For this reason some simple indicator had to be devised. A cork fitted around one of the screws of the mechanical stage receives a small indicator made of a thin blackened shaft of wood, at one extremity of which a sharp needle is bound. The square diaphragm in the eyepiece, which is readily cut out of black paper with a sharp knife, must be made of such a size as to allow a definite number of field-areas on the object to pass before the observer's eye for each revolution of the screw bearing the indicator. A card-board disk marked with divisions corresponding to fields, is held in place on a suitable stand by means of drawing tacks, the latter enabling one to change the disk for others bearing suitable divisions for other magnifying powers. The card is mounted on a perforated board, through the opening in which one is able to move the screw of the mechanical stage which bears the indicator. This board keeps the card from warping, and can be clamped at any elevation on a brass bar proceeding from the base, thus enabling one to tilt the microscope at any angle. The perforation in the board is bevelled on the outer side to enable one to manipulate the screw without cramping the fingers. There is no difficulty in centering the screw of the mechanical stage in this opening.

By means of this simple apparatus, which anyone can make for himself, one is able to accurately measure the size of the drop in fields. To facilitate this, one places the lamp-black ring as closely as possible around the margin of the dried sputum-drop—one can place it so near as to come within a distance measuring but the width of two or three fields. A drop may measure all the way from 180 to 220 fields in width.

To measure the diameter of the drop in fields is simple enough. One seeks that portion of the lamp-black ring to which one side of the quadrangular field forms a tangent. As the screw bearing the indicator only moves the mechanical stage in one direction one turns the screw until one reaches the inner side of the lamp-black ring. The indicator-needle is now fixed on the cork so that it points to 0 on the scale, and one proceeds to turn the indicator-screw until one reaches the inner margin of the ring on

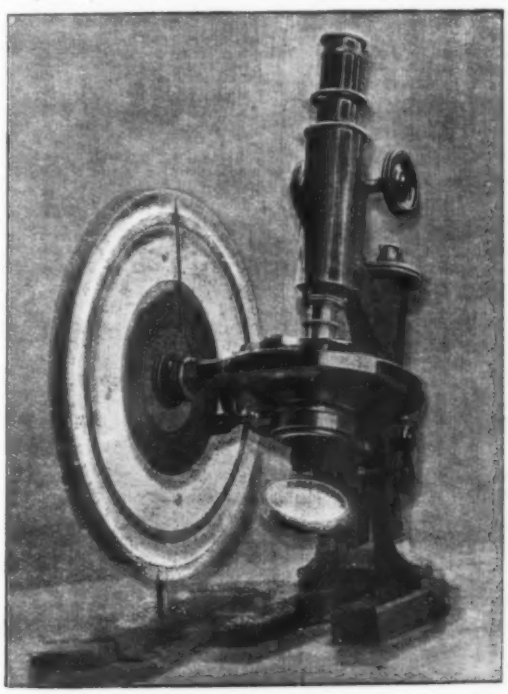

FIG. 4.

the opposite side. Deducting the distance between the inner margin of the ring and the periphery of the drop one obtains the diameter of the latter measured in fields.

METHOD OF COUNTING.

Although reasonably accurate results can certainly be obtained by counting the bacilli found in a large number of fields in different portions of the drop, to obtain the average number of bacilli to the field, and multiplying the number obtained by the number of fields representing the area of the drop,[1] I went to what may seem now the rather needless trouble of making my estimates more painstakingly. Beginning at the upper margin of the drop I counted all the bacilli found along its diameter.

[1] To give a case: A drop 200 field-widths in diameter is found to contain (as the result of counting 500 fields) on an average of 5 bacilli to the field. The calculation would be: $200^2 \times .7854 = 31416$ (area of drop in fields) $\times 5 = 157{,}080$ the number of bacilli in the drop.

I then shifted the object a given number of fields and counted along another line parallel to the first. This operation was repeated again and again until the margin of the drop was reached. It was found unnecessary to count usually more than sixteen "lines of fields" across a half-drop in this way, owing to the remarkably even distribution of the bacilli over the surface. The numbers of bacilli in the uncounted lines of fields were assumed to correspond to arithmetical means of the numbers found to exist in the actually counted ones, and by a simple calculation based on the numbers thus obtained the actual number of bacilli in the drop was closely approximated.

Registering the number of Bacilli counted.

I think all who have had to undergo the ordeal of counting a number of objects, be they minute or not, have had to overcome

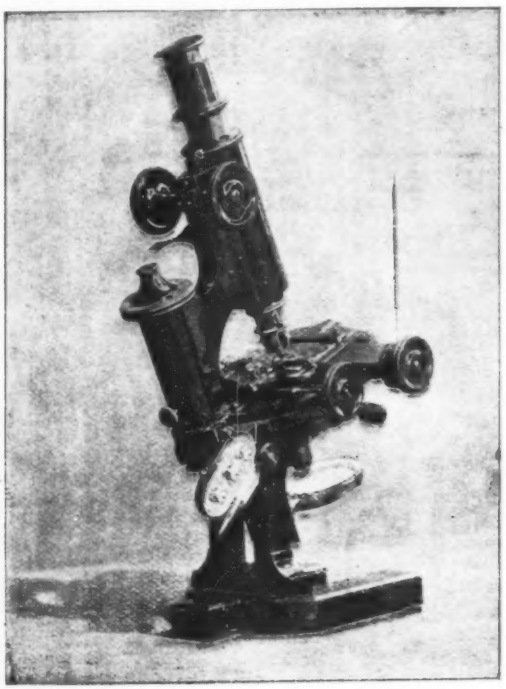

FIG. 5.

a tendency, after fatigue has set in, to count very irregularly. From personal experience I may state that after a time my mind persists in wandering off. To overcome this, and also to overcome the fatigue to the eye of constantly registering with a lead pencil on paper, thereby having to alter the accommodation from distant vision (when looking through the microscope) to near vision (when looking at the paper) the writer cast about for some mechanical device to aid him and fortunately came across a little counting apparatus which could not have been better to the purpose if it had been made to order. This little counting apparatus,[1] which is really intended for commercial purposes, is shown in figure 5 in its adaptation to the microscope, it being attached to the tightening bar at the joint. By using this apparatus the effort of constantly changing the accommodation of one's eyes is removed, much time is saved and practice soon gives one the dexterity of a telegraphist—one registers automatically. The hand does not need to leave the screw of the mechanical stage as the counting apparatus is easily reached with the thumb of the same hand, and the focussing being of course continued uninterruptedly with the left hand, one is able to count with great rapidity.

By causing the object to move in the one direction only, and counting the bacilli as the latter pass under the hair-line—*the counting can be interrupted or continued at any time, the field-indicator informing one of the exact position of the drop.* Depending on the number of bacilli to be counted one registers units, tens or hundreds. The apparatus registers 1000 units and by a sliding-scale attached above one can record ten thousand. As this little counting apparatus has proved quite invaluable to me and is probably not generally known to microscopic workers, I take this opportunity of strongly recommending it to general notice. The number of bacilli in each drop varied in these observations between 472 and 240,000, the individual clearly separated bacilli being counted readily in the latter.

The Calculation of the Number of Bacilli in a given Volume of Sputum.

Having carefully estimated the number of bacilli in a drop the rest is simple enough. One multiplies the number obtained by the number of drops to the cubic centimeter and this again by the number of cubic centimeters composing the suspension.

Observations on the Number of Tubercle Bacilli in the Sputum of Patients before and after Treatment with Koch's Tuberculin.

Before going on to describe the results obtained by the method described on the preceding pages, I deem it advisable to briefly notice the recent observations of two investigators in this same direction.

Amann[1] has examined the sputum of tuberculous patients at Davos during a period of three weeks following the tuberculin inoculations. He presumably employed the usual methods. He reports that usually the amount of sputum and number of bacilli increase as the result of the inoculations. The bacilli were observed to increase in 70 per cent. of the cases—in a few of these a subsequent decrease occurred. In four cases an immediate reduction of the number of bacilli was observed. In 40 per cent. of the cases the amount of elastic tissue was increased some time after the inoculations.

Immerwahr,[5] in his previously quoted publication, states that in thirty-two cases which had not improved under the Koch treatment no decrease in the number of bacilli was observed. In thirty-eight cases which had shown improvement the number of bacilli also remained unchanged. In twenty-one cases, mostly incipient phthisis, included under the head of "improved" the bacilli disappeared totally between the fourteenth and sixty-fifth day and have not again been found. In three cases where no bacilli were previously observed in the sputum these organisms made their appearance for a short time and disappeared again. In fifteen cases of incipient and moderately advanced disease of

1 "Field's Adding and Counting Register," pat. Jan. 8, 1878. Made by Schlicht and Field, 7 Exchange Street, Rochester, N. Y. The writer purchased two for a dollar a piece.

the lung bacilli never appeared, the diagnosis of tuberculosis of the lung being based on physical signs and the reaction following the use of the remedy.

A brief history of the case precedes each series of observations.

CASE I.

Annie J——, aet. 28, weight 107 lbs. (some years ago 133 lbs.). Married. Had coughed occasionally until six months ago when her cough became constant. Expectoration began about three months ago. Has moderate fever and is fairly well nourished. On percussion over the interscapular region impaired resonance observed more especially on the right side. Marked tactile fremitus over the same region. The right apex posteriorly gave crackling râles on coughing. In the upper interscapular region immediately above the angle of the scapula broncho-vesicular breathing, and on coughing sharp crackling râles heard. Left apex gave on deep inspiration very marked high-pitched tubular breathing and very liquid râles on coughing—these sounds being heard above the angle of the scapula and over the upper interscapular region. At the time the observations on the sputum were discontinued the patient showed improvement.

Date of observation.	Number of tuberculin inoculations received by the patient on or before the date given and the dose of remedy reached. Only nine inoculations given in this case.	Maximum temperature shown by patient during 24 hrs. (in Fahrenheit.)	Total amount of sputum (in cubic centimeters) for 24 hrs., the smaller number indicating the proportion of muco-purulent matter therein approximately (in cc.)		Remarks on the nature of the sputum.	Number of bacilli in the whole amount of sputum for 24 hrs.
Jan. 10.	.....	100.°	43	30	Tenacious, muco-purulent, greenish, streaked with grey and white masses.	2,081,922,400
" 11.	1st inoc., 1 mgr.	103.2°	...	...	.....	.....
" 12.	.....	100.6°	64	50	Muco-purulent, moderately tenacious; muco-purulent matter floating on viscid milky fluid, streaked with blood.	3,295,876,800
" 13.	2d inoc., 2 mgr.	101.5°	54	39	As before and *some elastic tissue.*	3,079,046,520
" 21.	8th " 5 "	102.2°	64	48	As before no blood, no *elastic.*	3,379,197,120
" 22.	9th " 5 "	102.8°	64	49	Muco-purulent matter greyish stringy, frothy. Some blood.	4,312,581,280
" 23.	.....	101.4°	51	40	As before.	2,494,599,120
" 30	.....	102.6°	66	51	As before and *some elastic.*	2,607,225,320
Feb. 1.	.....	103.°	58	40	As before some blood, no elastic.	3,110,100,000
" 2.	.....	102.2°	73	55	As before no blood, *some elastic.*	2,012,400,000
" 4.	.....	101.8°	73	51	As before blood and *elastic.*	2,263,450,000
" 9.	.....	101.4°	65	49	As before blood, no elastic.	2,936,443,800
" 12.	.....	101.°	66	44	As before.	2,322,936,000
" 16.	.....	100.7°	50	43	As before and *a little elastic.*	1,695,184,640
" 22.	.....	101.°	54	40	As before.	2,204,338,320
Mar. 1.	.....	102.°	64	39	As before.	1,853,728,900

CASE II.

Josephine T——, aet. 23, weight 124½ lbs., single. Cough began about four years ago. Had a few small hemorrhages. Nutrition very good. Temperature 98–100° F. A little less expansion over left clavicle than over right. On percussion high-pitched resonance on left side above clavicle, extending to upper border of second rib—posteriorly in supra-spinous fossa high-pitched resonance, the rest of lung clear. On auscultation left apex to 2nd interspace enfeebled and slightly high-pitched vesicular murmurs. Nowhere tubular breathing. Breathing accompanied by creaking râles on deep inspiration. In axilla breath sounds clear behind, enfeebled breathing at apex and a few crackling râles at end of expiration. The patient improved, gaining 8 lbs. during the time the observations were made.

Date of observation.	Number of tuberculin inoculations received by the patient on or before the date given and the dose reached.	Maximum temperature shown by the patient during the 24 hours (in Fahrenheit).	Total amount of sputum for 24 hours, the smaller number indicating the proportion of muco-purulent matter therein approximately. Measured in cubic centimeters.		Remarks on the nature of the sputum.	Number of bacilli in the whole amount of sputum for 24 hours.
Mar. 4.	.....	100.°	2	All	Muco-purulent greenish, adhesive.	37,921,424
" 5.	.....	99.5°	1.75	"	As before, only very adhesive.	20,144,256
" 6.	.....	102.2°	5	"	" "	165,814,000
" 7.	.....	99.8°	2.75	"	" "	131,785,632
" 8.	.....	99.4°	4	"	" "	120,484,800
" 9.	1st inoc., 1 mgr.	99.8°	6	5	" "	56,922,480
" 11.	.....	99.5°	2	1	Greyish, otherwise as before.	23,538,240
" 13.	4th inoc., 3 mgr.	101.1°	3.5	1.5	" "	62,036,100
" 15.	6th " 6 "	101.2°	6	All	" "	161,041,600
" 16.	.....	101.5°	3.5	1.5	" "	16,560,497
" 17.	7th inoc., 6 mgr.	98.7°	4.5	2	" "	283,457,601
" 18.	8th " 7 "	99.2°	3	All	Greenish, otherwise as before.	52,835,838
" 21.	11th " 4 "	99.1°	10	7	" "	3,697,200
" 22.	12th " 8 "	99.5°	5	All	" "	2,502,400
" 23.	13th " 10 "	99.8°	4	"	" "	369,600
" 24.	.....	99.2°	1	"	" "	469,648
" 25.	14th inoc., 10 mgr.	99.7°	5	4	" "	940,000
Apr. 4.	16th " 10 "	100.3°	4.5	All	" "	265,980

CASE III.

John H——, aet. 35, weight 132 lbs., married. Wheelwright by occupation. Cough began one year ago, after an attack of influenza, but did not become constant until 3–4 months ago. No expectorations or night-sweats until a few weeks ago. Looks healthy and well-nourished. Temperature 98–100° F. On examination found dullness from third to middle of fifth rib, and from left border of sternum to 3 cm. outside nipple. Over this area tubular breathing with sharp liquid râles on expiration and coughing. Bronchophony and pectoriloquy over an area 4 cm. in diameter above and to outside of nipple. Dullness toward axilla somewhat increased after inoculations with tuberculin. When the patient left at the expiration of two months he coughed less, his general condition was improved, his weight 136½ lbs.

Date of Observation.	Number of tuberculin inoculations received by the patient on or before the date given and the dose reached.	Maximum temperature shown by the patient during the 24 hours, Fahrenheit.	Total amount of sputum for 24 hours, the smaller number indicating the proportion of muco-purulent matter therein approximately. Measured in cubic centimeters.		Remarks on the nature of the sputum.	Number of bacilli in the whole amount of sputum for 24 hours.
Jan. 3.	.....	99.7°	32	32	Muco purulent, mummular adhesive, greenish with white masses interspersed.	70,474,880
" 4.	.....	99.2°	10	10	As before, only thicker and more adhesive.	.....
" 5.	.....	99.°	60	35	Muco purulent matter matter, floating on viscid milky fluid, with white cellular deposit.	52,794,000
" 6.	1st inoc., 1 mgr.	99.°	23	20	.....	15,400,000
" 7.	2nd " 2 "	99.5°	31	25	Do., *elastic tissue.*	26,334,000
" 8.	3rd " 5 "	100.2°	35	25	Do., *elastic tissue.*	32,105,920
" 12.	5th " 7 "	100.2°	34	16	Sputum whiter, frothy, fetid, no elastic.	35,676,300
Feb. 2.	15th " 13 "	100.°	58	20	As on 5th of January.	12,996,000
" 16.	22nd " 13 "	100.°	41	33	As before. *Small amt. of elastic tissue.*	19,608,400

The foregoing observations, though too few to justify us in drawing any general conclusions as to the effect of Tuberculine on the number of tubercle bacilli in the sputum, give us for the first time any idea of the actual numbers of bacilli which may be contained therein, and certainly suggest the advisability of using better methods in the future than heretofore, if scientific accuracy is to be at all considered.

A number of observations made by the writer before the method here described had been perfected, have been discarded. His inability to continue at present these investigations, coupled with the conviction that the chief value of this contribution would in any case lie in the description of the method employed, lead him to publish these results, few as they may appear, without further delay.

On the Question of the Multiplication of the Tubercle Bacillus in Sputum outside the Body.

It has not infrequently been stated that the tubercle bacilli multiply in sputum which has been left standing, but this has never been positively proven.

As putrefaction begins in sputum that has been left standing at room or body temperature the muco-purulent matter breaks up, and we have the bacilli much more evenly distributed through the fluid. When one now removes some of the sputum with a loop from the vessel in which it is contained and examines it, one has apparently a large increase in the numbers of bacilli—one can at times obtain very much the same result by the addition of caustic potash to fresh sputum.[1] To judge of whether the bacilli multiply or not in sputum outside the body will require a large number of observations and the writer believes that this can be best determined in the way about to be described.

1 Dr. Reese, Assistant Resident Physician, Johns Hopkins Hospital, has also observed this apparent increase when sputum was rendered homogeneous,—he was able to detect bacilli in this way when he had not been able to find them in unaltered sputum.

It will of course not do to try to divide a quantity of sputum into two parts to estimate the number of bacilli present in the one half immediately, and the number in the other half after it has been allowed to stand for some time—the objections are obvious. It will also not do to shake up the sputum with the idea of obtaining a rough distribution of the contained bacilli. We dare not alter the whole nature of the sputum by breaking up the muco-purulent masses and converting the whole into a foamy though perhaps even mixture. Tubercle bacilli might very well refuse to grow in sputum robbed at the beginning of its normal character. If there is danger of an apparent concealing a real increase, and if it is impossible to divide a given specimen into two parts, affording any assurance of the equal distribution of the bacilli, one must proceed as follows:

If the reader will turn to the table on p. 73 he will see that the variation in the number of bacilli from day to day in the sputum collected every twenty-four hours is very slight. If it were possible to obtain a similar case it would be the simplest thing to determine the question of the multiplication of the bacilli in sputum—the difficulty will only be to find a case. The way to proceed in such an event is to use the sputum of one day by way of control, the sputum of the next day to decide the matter of multiplication—that is, the sputum on control days to be examined immediately, that on alternate days to be placed in the thermostat or at room temperature for varying periods prior to being examined.

The writer regrets that limit of time has prevented him from making more than two observations in this connection—*both, however, point to an actual multiplication of the bacilli in standing sputum.* The experiments were made in the way above stated—and of course cases not undergoing the Koch treatment, that is, ordinary cases were chosen.

I.

Date of observation.	Total amount of sputum for 24 hours, in cubic centimeters.	Number of bacilli contained in the whole amount of sputum.	Number of bacilli to the cubic centimeter of sputum.	Time the sputum was left standing, and at what temperature.	Remarks on the nature of the sputum.
Feb. 16.	28	1,000,000,000	35,717,500	7 days at 17° C.	Muco purulent, greenish, very adhesive.
" 17.	24	443,233,280	18 468,053	*Control* (i. e. examined at once.)	Do.
" 18.	18	845,740,000	46,763,333	10 days at 17° C.	Do.
" 19.	56	438,922,800	7,837,907	*Control.*	Do.
" 20.	40	1,327,915,680	33,197,892	2 days at 17° C.	Do.
" 21.	61	342,830,400	5.620.170	*Control.*	Do.
" 22.	31	794,200,000	.....	*Control.*	Do.
" 23.	37	.....	.....	....	Do., *some elastic tissue.*
" 24.	47	4,258,060,800	.....	*Control.*	Do., *much elastic tissue.*
" 25.	56	911,872,000	.....	3 days at 17° C.	Do., no elastic.
" 26.	90	2,836,638,800	.....	*Control.*	Do., *much elastic an some blood.*

N. B.—It is particularly interesting to note the increase in the number of bacilli on the 22nd, leading up to great variations on subsequent days—*the very large numbers coinciding with the appearance of much elastic tissue in the sputum.* On account of this sudden variation in the numbers between the 22nd and the 26th of February, and their evident relation to the appearance of the elastic tissue, the writer has separated the last five observations from the first by a line, as he believes they should be considered apart. It is interesting to note the estimates of the number of bacilli to the cubic centimeter.

II.

Date of observation.	Total amount of sputum for 24 hours in cubic centimeters.	Number of bacilli contained in the whole amount of sputum.	Number of bacilli to the cubic centimeter of sputum.	Time the sputum was left standing and at what temperature.	Remarks on the nature of the sputum.
Mar. 18.	53	90,115,200	1,700,286	{ *Control* (i. e. examined at once).	But little mucopurulent matter, the sputum made up chiefly of pale yellowish cloudy viscid fluid. It did not change its character during these observations, and no elastic tissue appeared.
" 19.	60	257,741,880	4,295,698	2 days at 37° C.	
" 20.	54	12,489,552	231,288	*Control.*	
" 21.	57	67,943,232	1,191,986	2 days at 37° C.	
" 22.	50	62,120,448	1,242,409	*Control.*	
" 23.	37	153,172,800	4,139,805	4 days at 37° C.	
" 24.	70	168,366,400	2,412,377	*Control.*	

PROOFS OF THE ACCURACY OF THE METHOD.

The following observations will demonstrate the delicacy of this method of estimating the numbers of tubercle bacilli in sputum, and the constancy of the numbers of other organisms in drops of suspensions subjected to a similar shaking process. The observations clearly show the superiority of the drop to the loop-method in estimating the number of organisms in a suspension.

Four Calculations of the Number of Tubercle Bacilli in a given Amount of Sputum based on counts of two different drops of a series.

Case A.	Drop 1	gave	438,922,800
" "	" 2	"	404,103,600
Case B.	" 1	"	3,379,197,120
" "	" 2	"	3,277,994,304
Case C.	" 1	"	3,110,100,000
" "	" 2	"	2,809,620,000
Case D.	" 1	"	12,859,200
" "	" 2	"	12,996,000

Culture Experiments which control the Method.

The following experiments really form a part of another line of observations which the writer has been recently conducting together with Dr. A. A. Ghriskey (Assistant Resident Gynaecologist, Johns Hopkins Hospital) but they form such a perfect control of the accuracy of this method, that I deem it advisable to introduce them here. The numbers in the fourth column indicate the number of colonies which grew in roll-cultures, each being inoculated with one drop of a salt solution suspension of the organism named. *The number of colonies which grew in the cultures corresponded naturally to the number of organisms in the drop.*

No. of experiment.	Kind of organism in the suspension used.	Number of cultures made.	Number of colonies which grew in each culture.	No. of organisms counted in stained specimens of drops.
1.	B. anthracis.	2	7, 8.	9
2.	"	2	92, 89.	85
3.	Staphylococcus pyog. aureus.	4	1, 1, 1, 0.	
4.	" " "	2	171, 164.	
5.	" " "	4	118, 132, 132, 139.	
6.	Bacillus of Hog Cholera.	10	590, 579, 541, 513, 527, 500, 587, 577, 506, 598.	

NOTE ON THE GENERAL APPLICATION OF THE METHOD TO BACTERIOLOGY.

The writer believes that this method will prove of value in any experiments where it is desirable to introduce a definite number of organisms into culture media, disinfectants, etc., and that in point of delicacy it has proven itself beyond any question superior to the loop method for this purpose. One can readily control the number of organisms in a suspension by adding a number of drops containing an estimated number of organisms to a given amount of any fluid. Such a suspension can in turn be shaken, drops of it dried and the number to the drop estimated microscopically in a short time. Drops from suspensions in pure distilled water can be allowed to dry without spreading—the advantage being that the bacilli only cover a small area circumscribed by a suitable ring of lamp-black—all of them being fixed in place by the serum-film. Drops from suspensions in normal salt solution require the addition of a small drop of serum to them to permit of their being properly spread and to prevent large crystals of salt forming over the field so as to obscure the organisms. Large organisms such as B. anthracis are of course easiest to work with, as are also tubercle bacilli because everything else can be rendered absolutely colorless. With micrococci we have been only able to judge whether we have reached the right degree of dilution or not by the general appearance of the drop—owing to the difficulty of determining what are really organisms and what are not, as small round colored bodies often occur which look like micrococci. Bacilli on the other hand are unmistakable. The serum film retains the stain slightly but to so small a degree as not to interfere with the examination.

With such organisms as the tubercle bacillus, this method will enable the experimenter to determine the number he is inoculating into an animal in a way that has not been possible hitherto. Inoculations under such conditions will clearly show the difference in degree of virulence possessed by various organisms. It will clear up any relation which may exist between the number of tubercle bacilli in sputum and the progress of the disease and bring us a step nearer to solving the problem of the significance of involution and degeneration forms of bacteria.

Without considering the fact of greater accuracy, this method has many other advantages over the loop method—not the least of these being in the matter of rapidity. No contaminations have occurred in our culture experiments—this being partly due to the way in which the dropper was arranged for such experiments.

Dropping Apparatus for Culture Experiments.

Mounted on the same stand which supports the dropper used in the sputum experiments (see figure 1), is figured the apparatus used for culture experiments. The latter consists of a cotton-plugged, finely drawn-out and sterilized pipette passing through a sterilized rubber stopper into a large sized inverted funnel, which one sterilizes with carbolic acid. The funnel if desired can be surrounded with a wet curtain. Under the dropper a glass vessel

containing carbolic acid solution is placed into which the drops containing any dangerous organism, with which the operator is working, may be allowed to fall. Protected by the funnel the finely drawn-out dropper may be introduced into the testtube or other culture-vessel one is using, and the drop allowed to fall to the bottom of the same or into any fluid one may be working with. The drops can be made to fall so slowly that one can easily catch each or every other one as it falls without there being any danger of the dropper touching the side of the vessel, or of the drops falling in any other place but where desired, as the hands of the operator are perfectly steadied by pressing upward against the margin of the funnel.

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NOTES ON NEW BOOKS.

Fever: Its Pathology and Treatment by Antipyretics, by HOBART AMORY HARE, M. D., B. Sc. (*F. A. Davis, Philadelphia and London.*)

The author divides Antipyretics into three classes: 1st, Those which inhibit the production of fever—a class only comparable to the snakes of Ireland as he confesses there are none of this class; 2d, Those which decrease the production and increase the dissipation of bodily heat; 3d, Those which increase the radiation of heat so that the loss is greater than the supply. The majority of antipyretic drugs he considers to belong to the second class. The first class he believes to be an unattainable ideal, and the third unreliable and harmful, because the tissues are as rapidly destroyed under their influence as without the administration of any drug. Drugs of the second class are antipyrin, antifebrin, carbolic acid, salicylic acid and quinine. Drugs of the third class are cardiac sedatives like aconite and antimony. Bodily temperature may be varied by increased production and decreased dissipation of heat or by increased production and increased dissipation, the proper relation of the two processes being destroyed, or by normal production and decreased dissipation. Bodily temperature may be decreased by the exact reverse of these processes. Hyper-pyrexia is dangerous by its destruction of tissue and by its direct action upon the heart and nervous tissue. The author then proceeds to consider in turn the various antipyretics of the second class, antipyrin, antifebrin, thallin, phenacetine and salicylic acid, and gives a careful analysis of each. He speaks of their action on the nervous system, circulation, respiration, tissue waste, the urine, etc. The therapeutic uses of the drugs are also suggested and briefly commented upon. This work seems judiciously and systematically done. We are glad to notice that he recommends the use of antipyrin in typhoid fever "only when the cold pack (bath?) cannot be used or at the end of the cold application to prevent the temperature from bounding up after its depression."

His conclusions are of interest to every practitioner. . . . "Antipyrin stands to-day foremost in the ranks of the antipyretics, with antifebrin next, while thallin and phenacetine follow, with perhaps a preference for the latter. These conclusions are in regard to the reduction of fever. In pain the arrangement should somewhat be changed. Antipyrin still takes the lead but phenacetine is quite as useful as antifebrin and seems more safe. Thallin possesses hardly such power. In rheumatism, of course, the salicylates act better than the rest of the class of antipyretics, particularly in reference to the pain and the cure of the disease itself, but the others control the fever of rheumatism in a much more effective manner."

The book is a valuable resumé of the literature of the subject, and particularly well-suited to the use of students and practitioners.

Diseases of the Digestive Organs in Infancy and Childhood, with chapters on the investigation of Disease; the Diet and General Management of Children and Massage in Paediatrics, by LOUIS STARR, M. D. *Second edition. Illustrated.* (*P. Blakiston, Son & Co., Philadelphia.*)

Although this little volume of nearly 400 pages treats especially of the diseases of the digestive organs in infancy and childhood it contains other valuable chapters. The modes of examining children and their general management are fully dwelt upon. Careful directions are given for artificial feeding and the preparation of foods. The subject of bathing is also taken up and judiciously treated—as also clothing, sleep and exercise. It is gratifying to note that stomach washing is mentioned approvingly, and the indications for its employment are clearly given. The chapter on massage is a suggestive one, and the cases in which it is likely to be useful are clearly discriminated. In those portions of the book which relate to diseases of the digestive organs the various affections are treated of in a systematic and thorough manner. One chapter takes up affections of the mouth and throat and treats of the various forms of stomatitis, the disorders of first dentition, such as urticaria, strophulus, eczema and convulsions, and the gastric, intestinal, glandular, respiratory and other disorders which accompany the eruption of the permanent teeth. The list of possible disorders which accompany dentition is a long one—too long indeed for a book of this character. It may prove serviceable by suggesting dentition as an exciting cause in the diagnosis of extremely obscure affections in childhood. A following chapter treats of diseases of the stomach and intestines. Here under appropriate heads, gastric catarrh, ulcer of the stomach, softening of the stomach, gastro-intestinal catarrh, acute and chronic intestinal catarrh, entero-colitis, cholera infantum, dysentery, tubercular ulceration of the intestines, colic, constipation, etc., are fully described. This part of the book is of especial value by reason of its minute and specific directions for the preparation of food and the regulation of the diet of children. The medical treatment savors somewhat of polypharmacy but is in the main judicious. The presentation of a large number of ready-to-hand prescriptions and attractive formulae is apt to prove a stumbling-block to the young physician. Caseous degeneration and tuberculosis of the mesenteric glands, and affections of the liver and peritoneum also form the subject of full, and in the main, satisfactory chapters. The book as a whole is worthy of praise, and seems especially well adapted to the needs of the physician. It is attractively printed and well illustrated.

REPORT ON THE INOCULATION OF THIRTEEN GUINEA-PIGS WITH THE SPUTUM OF TUBERCULOUS CASES UNDERGOING THE KOCH TREATMENT.

By GEORGE H. F. NUTTALL, M. D., PH. D., (Göttingen) and JAMES HOMER WRIGHT, A. B.
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According to Fraentzel and Runkwitz,[5] Amann,[1] and more recently Feigel[4] and Immerwahr,[6] as well as other observers, microscopical changes which they consider indicative of degeneration are observable in the tubercle bacilli contained in the sputum of tuberculous cases undergoing the Koch treatment. It seemed advisable on this account to test the virulence of the bacilli in such cases by inoculations on animals,—for if these changes in the bacilli are really degenerative, then we may reasonably expect that the bacilli will show signs of attenuation by their affecting inoculated animals but slightly or not at all.

Guinea-pigs were chosen for these experiments because of the fact that they give more regular results than rabbits. Of 33 animals inoculated with sputum 15 died of septicaemia within the first few days after inoculation—the loss of many animals from this cause being an unavoidable part of such sputum inoculations. The following notes relate to 18 guinea-pigs, 5 of which were inoculated by way of control with the sputum of a patient who was not undergoing the Koch treatment—the 13 remaining animals having been inoculated with the sputum of different cases undergoing the treatment.

A brief outline of the history of each case[a] from which sputum was taken for the inoculations on the 13 last-named guinea-pigs is appended to the accompanying tables. The relative number of tubercle bacilli in the various sputa used is roughly indicated by the signs * (many), ** (very many), *** (enormous number), placed under the amount of sputum inoculated, noted in the third column. The sputum with which guinea-pig No. 13 was inoculated contained but few bacilli. Guinea-pigs Nos. 10–11 were inoculated hypodermically with a salt solution suspension of small cheesy almost spherical masses measuring respectively $\frac{1}{4}$ and $\frac{1}{3}$ cm. across—these masses were almost pure cultures of very small beaded tubercle bacilli and represented an enormous number of these organisms. The cheesy masses were broken up in a small sterilized mortar and pestle (made of glass tubing) into which broken glass had been introduced. It was found that the most satisfactory way of inoculating guinea-pigs with sputum was to inject the latter hypodermically with a large syringe.

CASE I.

William P. L——, aet. 50, weight 114½ lbs., single. Machinist on ships. Admitted to Hospital December 11, 1890. Began to cough 9 months ago, at which time he weighed 145 lbs. Cough not severe, expectoration scanty, mucoid. No haemoptysis. Sputum examined 6 months ago contained tubercle bacilli but no elastic tissue. Four months ago his weight had fallen to 106 lbs. On treatment at the time the patient's condition improved. On admittance the patient appears but slightly emaciated, looks well. Temperature 99–100° F. Chest fairly broad and quite deep. Total expansion 5 cm. Percussion on the right side over first rib and second interspace and third rib gives high pitched resonance—not definite dulness. Slightly defective resonance in clavicular and supra-clavicular region. Rest of lung clear. On the left side slightly impaired resonance in supra-spinous fossa, lung clear below. In inter-scapular region on both sides resonance a little skodaic. Fremitus a little more marked in the left than right mammary region. Behind, fremitus a little more marked on left than on right side.

On auscultation, breath sounds nowhere intense. At right apex at end of inspiration a few crackling râles. At left apex both on in- and expiration distinctly cavernous and on coughing crackling râles heard. No other appreciable alterations in front, except that expiration is everywhere a little prolonged. Behind at right apex rather deep broncho-vesicular breathing, fine crackling râles at end of inspiration, toward base breath-sounds become louder. On the left side breathing at apex approaches cavernous, a few râles on coughing—breath sounds loud and clear at base. Expiration on both sides distinctly prolonged.

Other organs normal. Patient improved under Koch treatment, coughed less, expectoration ceased, weight rose 3 lbs. On the 8th of January, fewer râles, the condition of lungs otherwise about the same. Patient left Hospital February 26, 1891.

CASE II.

K——, aet. 29, weight 99 lbs., married. Admitted to the Hospital December 15, 1890. Cough began in the autumn of 1888, with loss of flesh and bacilli in the sputum. In January, 1890, patient had influenza after which she developed signs in the lungs. Had bronchitis and clear evidence of cavity formation at right apex. She improved subsequently. On entering the hospital a cavity at the right apex and some consolidation of left apex observed—the rest of the lungs presenting no abnormal signs. The patient left unimproved, February 16, 1891.

CASE III.

Robert D——, aet. 34, weight 155 lbs., single, laborer. Admitted to the Hospital December 24, 1890. Began to cough about four months ago. Coughed but little, with occasional appearance of blood. Complains of but slight fevers at night, no sweats. His weight in summer was 170 lbs.—has been working hard. Patient strong and healthy looking. Temperature 101–102.8° F. Chest well formed—circumference 38 inches, expansion ¾ inch. Tactile fremitus slight and equal on both sides. Percussion on right side at apex and over clavicle, gave slightly deficient resonance. In the outer mammary region and extending into extreme upper axilla, slight dulness. Left lung clear in front and behind. Right lung behind at extreme apex clear on percussion, below and to outer side of spine of scapula defective resonance—the rest of the lung clear. Auscultation, on right side in front clear everywhere, in upper axillary region tubular breathing very marked—bronchophony and whispered voice. On coughing a few crepitant râles. Behind, above spine of scapula clear, over the area of dulness above noted—the same signs as in axilla. Other organs normal.

The patient left the Hospital on February 24th much improved in condition, having gained 7¾ lbs., the cough almost gone, the expectoration reduced to about 2 cc. each 24 hours, and containing but few bacilli.

CASE IV.

Kate J——, aet. 32, weight 91 lbs., married. Admitted to the Hospital December 12, 1890. Troubled with cough for the last four years during the winter. Hardly any expectoration until the spring of 1890—the sputum thick and once or twice tinged with blood. Very little sweating at night, does not complain of fever. No loss of flesh, no gastric symptoms. The sputum on admission amounted to 20–40 cc. in the 24 hours, contained elastic tissue and many bacilli. Temperature normal. Pulse 80. Respirations quiet. Expansion equal and good on both sides. Tactile fremitus equal and normal. Left clavicle a little more prominent than right—slight flatness on that side. On percussion above clavicle and in infra-clavicular region on the left

[a] Abstracted from the Clinical Records of the Johns Hopkins Hospital.

I.

No. of Experiment.	Date of inoculation of animal with sputum.	Amount of sputum inoculated.		Weight of animal (in grammes) at time of inoculation and at death or shortly before death.	No. of days animal lived after inoculation.	*Post-mortem Notes.* Including microscopical examination of tissues by means of sections and smear-preparations.	Positive or negative result expressed by signs.
1	Dec. 21.	1.5 cc.	.....	556–315	46	Seat of inoculation ulcerated. Inguinal and mesenteric lymph-glands enlarged. Liver and spleen tuberculous, sanguineous fluid in peritoneum. Lungs pneumonic. Tubercle bacilli found in liver, spleen and lymph-glands.	+
2	Dec. 21.	1.5 cc.	.....	545–385	50	Inguinal and mesenteric glands enlarged and caseous. Liver, spleen and lungs presented tuberculous nodules. Tubercle bacilli found in all the organs mentioned.	+
3	Dec. 21.	1.5 cc.	.....	648–420	26	Lymphatic glands generally enlarged. Left axillary gland enormously enlarged forming pus-sack. Spleen tuberculous. One tubercle on edge of lung. Bacilli found in lymph glands and spleen.	+
4	Dec. 21.	1.5 cc.	.....	437–265	25	Found dead, its abdomen eaten open by other guinea-pigs. Animal much emaciated. Lymphatic glands generally tuberculous—one axillary gland as in preceding case. Bacilli found in glands.	+
5	Dec. 21.	1.5 cc.	.....	289–204	26	Lymphatic glands generally tuberculous. Miliary tubercles in lung and spleen—bacilli found.	+

II.

No. of Experiment.	Date of inoculation of animal with sputum.	Amount of sputum inoculated (in cubic centimeters).	No. and dose of tuberculin inoculations received by patient on or before the date given.	Weight of animal (in grammes) at time of inoculation and at death or shortly before death.	No. of days animal lived after inoculation.	*Post-mortem Notes.* Including microscopical examination of tissues by means of sections and smear-preparations.	Positive or negative result expressed by signs.
1	Jan. 4.	1.5 *	8 inoc's, 4 mgr. (*Case II.*)	417–280	18	No signs whatever of tuberculosis, no bacilli found anywhere. Died from chronic septicaemia.	–
2	Dec. 21.	1.5 * *	9 inoc's, 8 mgr. (*Case I.*)	515–300	59	Cheesy mass at seat of inoculation containing tubercle bacilli. Miliary tubercles in lung, liver and spleen. Lymphatic glands caseous—tubercle bacilli found in the tissues named.	+
3	Dec. 21.	1.5 * *	9 inoc's, 8 mgr. (*Case I.*)	173–205	34	Hemorrhage from nose. Seat of inoculation ulcerated. Inguinal, bronchial and mesenteric lymph-glands enlarged, tuberculous. Clot in trachea. Miliary tubercles found in lung, liver and spleen—tubercle bacilli found in latter and in lymph glands.	+
4	Dec. 21.	1.5 * *	9 inoc's, 8 mgr. (*Case I.*)	497–312	64	Inguinal and bronchial glands much enlarged, caseous. Tubercles in liver, spleen and lungs, bacilli being found therein as also in the caseous glands. Intestine congested in places.	+
5	Jan. 29.	3. *	15 inoc's, 11 mgr. (*Case III.*)	275——	17	Seat of inoculation ulcerated. Lymph-glands enlarged and caseous. Lungs congested, contain small tuberculous nodules. A few small tubercles in the liver. Spleen apparently normal. Bacilli found in lungs, liver and lymph-glands.	+
6	Jan. 16.	2 *	16 inoc's, 6 mgr. (*Case II.*)	440–280	23	Indurated ulcer at seat of inoculation. Inguinal glands enlarged, caseous. Miliary tubercles in lung, spleen and liver. Tubercle bacilli found in caseous glands, lung, liver and spleen.	+
7	Jan. 16.	2.5 *	16 inoc's, 6 mgr. (*Case II.*)	330–205	18	Showed signs of paralysis two days before death. Seat of inoculation ulcerated. Inguinal glands on side inoculated and mesenteric glands enlarged. Lungs pneumonic. Spleen enlarged, tuberculous, highly pigmented. Bacilli found in spleen and glands.	+
8	Feb. 10.	2.75 *	18 inoc's, 11 mgr. (*Case V.*)	575–370	19	Seat of inoculation ulcerated. Lymph-glands enlarged. Liver, lungs and spleen tuberculous, contained bacilli.	+
9	Jan. 8.	2.5 *	20 inoc's, 19 mgr. (*Case I.*)	509–495	22	No signs whatever of tuberculosis. Small necrotic areas in liver. Spleen contained much pigment. Died from chronic septicaemia.	–
10	Jan. 24.	* * *	21 inoc's, 7 mgr. (*Case II.*)	270–180	36	Seat of inoculation ulcerated. All the lymphatic glands, as also liver, lung and spleen, showed tuberculous tissue and contained tubercle bacilli.	+
11	Jan. 28.	* * *	23 inoc's, 7 mgr (*Case II.*)	260–210	33	No evidence of tuberculosis. Lymph glands enlarged. Liver, apparently normal. Spleen highly pigmented. Lungs pneumonic.	–
12	Jan. 29.	2. *	27 inoc's, 36 mgr. (*Case IV.*)	250–210	18	Seat of inoculation ulcerated. Lymphatic glands enlarged. Liver, apparently normal. Spleen highly pigmented. Bacilli found in glands.	+
13	Jan. 29.	1.	29 inoc's, 36 mgr. (*Case VI.*)	510–340	17	Large ulceration at seat of inoculation. Lymph glands enlarged. Liver, apparently normal. Spleen pigmented. Lungs pneumonic. Tubercle bacilli found in lymph glands.	+

side, high pitched note extending as far as the third rib. Behind, the note at left apex flatter than on right side. On auscultation on the left side breath sounds observed to be feeble, somewhat tubular particularly on expiration, very few râles heard on quiet inspiration—on deep inspiration many râles of medium size, larger and louder on coughing were heard. Behind, on coughing, râles heard as low as the middle of the scapula. A few râles at apex as well as in inter-scapular region. Right lung clear on percussion, throughout. A few râles in front at right apex.

Patient improved under treatment gaining 13¾ lbs. Left the Hospital April 4, 1891.

Case V.

John H——, aet. 35, weight 132 lbs., married. Wheelwright by occupation. Admitted to the Hospital January 2, 1890. Cough began one year ago after an attack of influenza, but did not become constant until 3–4 months ago. No expectoration or night-sweats till a few weeks ago. Looks healthy and well nourished. Temperature 98–100° F. *Examination:* Dulness from third to middle of fifth rib and from left border of sternum to 3 cm. outside nipple. Over this area tubular breathing with sharp liquid râles on expiration and coughing. Bronchophony and pectoriloquy over

an area 4 cm. in diameter above and to outside of nipple. Dulness toward axilla somewhat increased after inoculations with Koch remedy. When the patient left at the expiration of two months he coughed less, his general condition was improved his weight being 136½ lbs.

CASE VI.

Kate K——, aet. 30, weight 111½ lbs., milliner. Admitted to the Hospital December 12, 1890. Complained of slight cough but did not have much fever. On examination, expansion in right infra-clavicular space found defective. Resonance higher in pitch as low as third rib—the breath sounds being feeble. Expiration somewhat tubular. Moist râles large and medium sized as low as fourth rib. Behind, defective resonance in supra-scapular region—moist sounds as low as middle of scapula. Left lung uninvolved. Temperature on admittance 98.2° F. Bacilli in sputum in small numbers. No elastic tissue. Up to about the 15th of February, 1891, patient showed improvement—cough moderated, sputum lessened in quantity and weight rose to 118½ lbs. At time of writing patient is still in the Hospital, expectoration has again increased, her condition not improved.

Of the 13 guinea-pigs inoculated with the sputum of patients undergoing the Koch treatment, (see Table II) ten became tuberculous. From this we may conclude that the bacilli in the sputum were still virulent. We have the following grounds for not laying too much weight on the three negative results obtained.

Völsch[11] (1889) observed that the development of tuberculosis was considerably retarded or even checked when rabbit-septicaemia bacilli introduced with tuberculous sputum multiplied in the animal inoculated. Depending upon the number of rabbit-septicaemia organisms in the sputum, as also their rate of development, the septicaemia produced was either chronic or acute—he coincided with Smith[10] (1886) in the latter observation.

In this connection it is important to note that Welch[12] has observed under normal conditions a wide variation in the degree of virulence of the organism of sputum-septicaemia. Depending upon the grade of virulence of the organism, the septicaemia was rapid or slow, or the animal remained quite unaffected by the inoculation.

This antagonism between two different pathogenic organisms in the body of an animal has also been observed in other cases to lead to recovery or retardation in the progress of a disease.

Emmerich and Mattei[2,3] showed that a number of animals inoculated with bacillus anthracis did not die as is usual of anthrax if they had been previously or subsequently inoculated with cultures of staphylococcus pyogenes aureus—the introduction of the latter organism in these cases retarded or completely checked the growth of anthrax bacilli in the animal. A large number of anthrax bacilli were completely destroyed in some cases.

Pawlowsky[9] followed out this line of research. He in a number of instances cured localized anthrax by inoculating Friedländer's pneumo-bacillus. Staphylococcus pyogenes aureus and bacillus prodigiosus did not have as much effect. When the anthrax infection was of a general character, inoculation with pneumo-bacillus retarded the progress of the disease and in a few cases a cure was produced.

Kostjurin and Krainski,[8] in a preliminary note entitled "On the action of putrefaction, and tubercle-toxines on animals and their influence on experimental tuberculosis," state that it is highly probable these bodies introduced subcutaneously in an animal retard the further development of tuberculosis and may render an animal immune against renewed infection—besides this, they seem to render the tuberculous process simply a local one and promote caseation.

The observations of the foregoing experimenters show us that it is necessary to be cautious in interpreting our results, particularly when negative ones are in the minority. From the few experiments here given it is difficult to form a positive opinion. We are inclined to conclude that as long as the majority of our animals died with tuberculous lesions the tubercle bacilli were not attenuated. A certain number of the results in such experiments must inevitably be obscure as we are always dealing more or less with unknown quantities when we inoculate an animal with such a septic putrefactive mass as tuberculous sputum. There seems, however, to be no other way out of it than to carefully continue this line of experimentation on a larger scale *as mere microscopical observation cannot determine the matter*, and we have no other means at hand of settling the question than by direct inoculations of animals.

It will be remembered that Koch[7] in his second communication said, "Only this much is certain, we have not to deal with a killing off of the tubercle bacilli in the tissues—it is the tissue which contains the bacilli which is acted upon by the remedy."

The writers regret to state that these inoculations were made before the method for estimating the actual number of tubercle bacilli in sputum, described in an accompanying article, had been perfected, and consequently as in all similar experiments as yet made, an unknown number of organisms was introduced into the animals with the sputum.

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ON NERVE DEGENERATION IN SOME SYPHILITIC GROWTHS.

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(A Paper read before the Johns Hopkins Hospital Medical Society, March 16th, 1891.)

During the past winter Dr. Councilman called my attention to some nerve bundles in a hard chancre he was examining. In this section, which was stained with safranin, the axis cylinders appeared to be in great measure absent, the myeline glassy and atrophied, while the connective tissue elements, especially nuclei, seemed to be little or not at all increased. A glance over the literature on venereal sores gave no information, except of the absence of all mention of nerve changes, and after a further examination of other sections from different parts of the sclerotic mass, always finding the same condition, I undertook at his suggestion to make a study of a number of chancres, chancroids and syphilitic growths, to determine if this state of the nerves was a constant feature.

After some necessary delay six chancres, four chancroids, five gummata, one condyloma and a syphilitic papule were obtained from the clinics of Drs. Halsted and Brown, and for comparison, a piece of skin adjoining an epithelial growth on the cheek, a number of tumors, principally sarcomata, several clippings from the edges of old varicose ulcers, a cicatrizing wound from a dog, and a normal foreskin from the circumcision of a two year old child. These, with three exceptions, two chancres in alcohol and a chancroid in Müller's fluid, were hardened in Flemming's mixture. Two other sores from the foreskin were excluded on account of uncertainty in the micro-diagnosis.

A difficulty was now experienced in obtaining clear pictures of the minute skin nerves. Alcohol sections stain satisfactorily for all other tissues but the nerves, which are rarely brought out distinctly. In Müller's fluid preparations, stained with Weigert's hematoxylin, the nerves are stained alone, and their relation to the surrounding elements is not well shown; and besides, in longitudinal sections, no distinct view of the axis cylinders can be obtained, while the tingeing was found to be far too inconstant for actual use. With Flemming one is reduced to safranin alone, and then it is a matter of difficulty to readily distinguish the small nerve filaments among the mass of equally red tissues. Gold was also tried with a very unsatisfactory result.

After considerable experimenting I found that by using considerable heat in the preparation of Weigert's hematoxylin, and also by slightly changing the proportion of the ingredients, a marked change in the staining properties of the resulting fluid was obtained—at least with Flemming preparations—and that the nerve fibres were now equally tinged. The following receipt was found to be the most constant. Fifty cc. of distilled water are boiled freely for ten minutes, and from one and a half to two cc. of a 10 per cent. tincture of hematoxylin added, and the boiling continued for a minute; then two cc. of saturated solution, lithium carbonate, are added, well shaken; the flask tightly corked and allowed to cool gradually, and the following morning it is ready for use. This fluid spoils readily on exposure to air, and should always be kept tightly corked.

For tingeing, the sections are placed over night in a closed vessel with sufficient saturated solution of the acetate of copper to cover them, then next morning they are carefully, in the same vessel, heated on the water bath to a temperature of 35° C., and allowed to stand at that temperature for ten minutes; are then allowed to cool, and are rapidly washed out in a large quantity of water; then go into the staining fluid, and again heated to a temperature of 35° to 40° C. over the water bath, for from fifteen to thirty minutes, according to the color desired, removed, and allowed to stand fifteen or twenty minutes; then washed out with water; then go into the ordinary decolorizer of borax and potassium ferricyanide, where they usually obtain the desired color in from five to ten minutes, and are washed out twice in a large quantity of water, dehydrated, cleared in oil of bergamot and mounted in zylol-balsam.[1]

The epithelium is cleanly outlined, of a smoky color, with nucleus and nucleolus distinct; the granulation cells are almost black; the molecules jet; connective tissue is stained a light yellowish-brown; fibrin almost black. The vessels are very distinct; the lining membrane of certain lymph spaces very dark. The white corpuscles are stained blue, with nuclei distinct; nuclear figures are black and beautifully shown. The axis cylinders of the nerves are black; myeline a very light blue, sometimes a little smoky; the inter-tubular connective tissue yellow; all nuclei dark brown or black.

For comparison and correction, safranin, sometimes borax carmine, when it could be made to stain, was used.

In the normal prepuce the nerves were abundant, and with this modified staining fluid the whole bundle under low power assumed a somewhat brownish tint; with a higher, the axis black, myeline faint blue, all the connective tissue portions of the nerve yellowish-brown. The lymph spaces, especially that immediately internal to the sheath, are well shown. The nuclei are not prominent, but clear. A large number of comparisons with sections of normal nerve trunks showed this condition to be constant, and when doubt arose, all sections of diseased nerves in the tissues were compared with those of the prepuce. Cross sections are generally preferable for description, the extremely sinuous course of the skin nerves rendering examination of a longitudinal cut often misleading.

In the inflamed tissues used for comparison, no nerve lesions were found in the sections from the margins of chronic ulcers, or in the inter-muscular nerves from the cicatrizing wound; in the majority of the tumors the nerves were perfectly sound, even though running through the new formation; occasionally there is a minimum amount of connective tissue proliferation. The most marked example of this proliferation, which would have escaped any but the closest examination, was in the epithelioma excised from the cheek. The sections did not involve the cancerous growth, but were from the margin, where there was but a trifling amount of small cell infiltration. The sheath of these nerves is somewhat thicker than healthy ones, with corresponding narrowing of the peri-fascicular lymph space, and many prominent nuclei are to be seen among the inter-tubular bundles; the axis cylinder is, however, distinct, and present in every myeline

[1] Very creditable preparations of the nerves and tissues may be readily made in much less time, by increasing the temperature of the copper and hematoxylin solutions to 60° C., and it is possible to finish the mounting within forty minutes of the time of immersing the sections in the copper solution; though the finer details suffer somewhat.

sheath, the substance of Schwann colored light blue and nowhere broken up into drops.

In the six chancres examined morbid changes were found in each and every case, only differing in degree. The length of time the sclerosis has existed, seems to have had little reference to the amount of nerve disease; for example, a sore that had been on the penis for three weeks had changes much more intense in degree than another of four weeks standing. The amount of degeneration seems to depend not on the age of the chancre, but on the density of the induration, and the extension of the small cell elements along the courses of the blood vessels. Rarely a nerve filament is to be found in the chancre proper, but in the deep seated tissues underlying it.

All the specimens obtained were from the prepuce and glans. I cite as illustrative examples the two following cases, which correspond so closely with the others that it is unnecessary to give them in detail.

3631. John G., aet. 48, German by birth. The sore first appeared three weeks after connection. Great induration, slight secretion. Diagnosed hard chancre.

Micro-examination. Typical initial sclerosis. The proliferated connective tissue is more homogeneous and refractile than normal, inclosing in its meshes round cells. The papillae of the corium are much thickened and swollen. Fibrin is present throughout the tissue. There is an intense degree of endarteritis. Hardly any destruction of the layers of the dermis is present, only infiltration.

The nerves present a number of variations. Those not imbedded in the granulation masses, are most often normal, or approximately so. Where there is slight swelling of the inter-tubular connective tissue, there are always one or more myeline tubes becoming glassy. This glassy state seems to be the first alteration in the myeline.

In those surrounded by masses of small round cells, the lymph space within the sheath is usually invisible, occasionally greatly narrowed. The sheath itself is hardly at all thickened, while the connective tissue fibres between tubes are much broadened, though the increase of nuclei is very slight. The myeline tubes present, are often confined to the periphery of the fasciculus, and in a bundle that should contain from 30 to 40 fibres, but 14 were present; and of these, five had no visible axis cylinder. A few narrow black irregular lines are to be seen in the places formerly occupied by the medullated tubes, and may possibly represent the membrane of Schwann, which is stained somewhat darkly by this method. In longitudinal sections the few remaining myeline tubes have very irregular contours, and more often have the central filament absent than present.

6232. John T., aet. 19, black, laborer. Has had a sore on penis for one month of uncertain incubation. Base very hard. Secretion slight. Continuous headache. Diagnosed hard chancre.

The microscopic sections show the typical Hunterian chancre: very slight erosion of the epithelium, connective tissue framework much proliferated, dense granulation tissue, marked endarteritis, and fibrin everywhere.

The majority of the nerves lie deep down beyond the region of the granulation cells, and are normal in respect to their fibres, lymph spaces and nuclei.

Others in closer relation to the round cells, are beginning to show changes in the myeline, and non-distinctness of the cylinders. In a rather large bundle running perpendicularly to the surface, and presenting a number of views both longitudinal and transverse, the lowermost cuts have no lesions visible in them, while the higher ones, imbedded in granulation cells, do not stain so deeply, the myeline is a little glassy and irregular in contour, the cylinders not so clear, and the lymph spaces reduced in size.

Individual peculiarities in single bundles are not lacking. In minute fascicles composed of three or four tubes, these tubes have sometimes entirely vanished, leaving only a bundle of transparent connective tissue, with occasionally a large irregularly shaped cell apparently attached to the margin of the connective sheath. Sometimes in a larger bundle the tubes may have disappeared up to four or five, and among them will be a single one four or five times larger than the others, and about three times as large as a normal one. In the centre of this fibre is always a number of fine black molecules. The lymph space does not vary much in highly degenerated bundles; it is either completely absent, or there is a small oblique slit at one side, and generally near this, the remaining tubes are congregated. If fresh, alcohol sections stained with hematoxylin and eosin do not differ in any way from the modified Weigert, but old specimens are useless, because the structure of the bundles becomes very indistinct.

The genesis of the lesion in the Hunterian chancre I take to be as follows: There is first disturbance of the arterial circulation superinduced by the intense endarteritis, and consequent changes in the lymph flow; then follows swelling, more or less pronounced, of the connective tissue elements, especially of the inter-tubular, and subsequent nutritive changes in the axis cylinder and myeline, the first disappearing in the part involved, the latter becoming glassy, rarely granular: finally, as the lack of nutriment continues, the tubes atrophy more or less completely, and are replaced by the swollen connective tissue, which always seems to require less nourishment than more highly organized structures. The rapid growth of the small cell formation is undoubtedly no unimportant factor in the case, assisting and intensifying the atrophic process by direct pressure from all sides on the nerve. This is shown by the fact that the nerve bundles are very seldom degenerated unless they are surrounded on all sides by the new formed cells. That the process is more atrophic than inflammatory is shown by the lack of profuse increase in the inter-tubular connective tissue nuclei, they very rarely becoming numerous, though their number is always somewhat above the normal.

The extent of the nerve lesion is very limited, it is never met with beyond the region of endarterial inflammation and small cell infiltration. A nerve that may be completely degenerated in the higher regions of the dermis, may be so nearly normal in the lower as to present no microscopic change.

Gummata approximate very closely to the structure of the hard chancre, but usually their situation is unfavorable to the presence of abundance of nerves, either in, or adjacent to the tumor. Five of these growths were collected, two stained so badly (123) as to be useless for fine details; another, a subcutaneous growth on the thigh, contained no nerves in the sections examined. This reduces the list to two, one from the testicle (TP), the other from the leg (127). In the latter the nerves are very scant; one large bundle deeply situated in the connective tissue, surrounded on all sides by granulation cells, has the following appearance: there is a medium calibre vessel running by the side of the nerve, with pronounced endarteritis and narrowing of the lumen. The sheath does not appear swollen, but the lymph space has almost vanished. Many nerve tubes are indistinct, glassy, with the axis cylinders

either not present or very indistinct, apparently atrophied, others have a perfectly natural appearance. The normal are stained slightly darker than the atrophied. The inter-tubular connective tissue seems broadened where the fibres have in part disappeared, but there is no extensive increase of nuclei.

In the other tumor, two nerve bundles outside and beyond the small cells are perfectly natural, while two smaller longitudinal and cross sections within the granulation region are distinctly degenerated, and correspond closely in appearance with those from the leg. It is almost impossible to decide exactly where the degeneration of the nerve begins, the spurs of new formed cells following the courses of the blood vessels for long distances beyond the tumor proper, preclude all possibility of tracing the nerve, and ascertaining how far distant from the growth the degeneration advances. Once or twice when the section lay on the extreme edge of the infiltration around the tumor, and a nerve could be found with granulation cells surrounding it, near a blood vessel, the nerve would be partly degenerated, while in the more healthy tissue beyond they would be sound.

The two other syphilitic new growths examined contained greater numbers of nerves, but in proportion to their number, had fewer entirely degenerated bundles.

The syphilitic papule was from the neighborhood of the anus, and was of some weeks standing. The initial lesion dated back five months. The vessels of medium calibre are much thickened, and are imbedded in small areas of newly formed round cells. The papillae and connective tissue stroma are much hypertrophied. The nerves differ in appearance according to whether they are completely imbedded or only situated on the margin of the granules. In the latter case the sheath is denser on the side toward the new formation than on the other, the lymph space, while narrow, is still present; the inter-tubular connective tissue is not increased perceptibly in density, nor are the nuclei very prominent, while the nerve tubes retain the myeline and cylinder normally colored. On the other hand, in those completely surrounded, the sheath, while little thickened, has now no lymph space within it, the myeline tubes are indistinct, but few axis cylinders are seen in the bundle, and these seem to have dwindled to a minute thread, while the myeline itself is shrunken to a considerable degree. The nuclei are a little above the normal in number; the connective tissue bundles broad; the whole fascicle stains less deeply than it should.

The condyloma was also from the anus of a child with a well marked history of hereditary syphilis. The papillae of the skin are extremely hypertrophied and infiltrated. The section, which is a good sized one, contains a large area of fatty tissue underlying the inflamed papillae. In this part the nerves, which are also less intimately in connection with the vascular system than in the superficial areas, are normal. Those subjacent to the infiltrated papillae vary in degree of degeneration, the tubes of several fine bundles contain no cylinders, with the myeline so far shrunken as with difficulty to be perceived; where seen in longitudinal view shrunken and very finely granular. The connective tissue is broad, homogeneous, with occasional large nuclei among the fibres. The sheath is not thickened, sometimes a large granular cell appears clinging to the inner margin. The lymph space is invisible. With large bundles the appearance is similar, but a proportion of the tubes are normally medullated, and contain the axis cylinder.

The structure of the chancroid, though much resembling the chancre, differs in some important details. There is destruction, not hypertrophy of the corium, there is but little proliferation of the connective tissue, the small cell growth is more diffuse and less dense, finally, the endarteritis is not such a marked feature. These differences make an essential change in the aspect of the nerve bundles. In two of the four examined there was absolutely no lesion of the nerves; in one of the others, just underneath the ulcer itself, a few nerve bundles show an increase in the number of connective tissue nuclei, but the tubes are perfect, and there is no contraction of the lymph space; in the last one, several bundles deeply imbedded in rather dense masses of granule cells show a lessening of the lymph channel, and absence of a few axis cylinders, with slight changes in the tingeing of the myeline.

For an answer to the question why the nerves should degenerate in syphilitic and not in simple inflammations, the following replies may be made:—the infiltration of cells of an embryonic type is generally denser, and the proliferation of the connective tissue elements more of a sclerotic type than in simple ulcerations, therefore more liable to change nutrition by compression; secondly, the endarteritis is more pronounced; thirdly, the syphilitic virus permeating the tissues may in itself cause a predisposition to nerve degeneration, by its general action in lowering nutrition, but the stoppage of the arterial supply and the dense cell proliferation within the meshes of a hypertrophic connective framework, which permits of little expansion and causes the woody feeling distinctive of the true chancre, are most probably the potent agents in producing this mixed form of interstitial-parenchymatous neuritis.

The conditions were too unfavorable to make much out of the nerves between bundles of two or three fibres and the end apparatus; tactile bulbs were now and then met with, Pacinian bodies quite frequently, especially in the glans. With the modified Weigert method, the terminal filament of the nerve tube no longer appears pale and unstained, but opaque and black as the axis cylinder itself, the capsules retaining their usual aspect.

Baltimore, September, 1890.

HOSPITAL PLANS.

Five essays relating to the construction, organization, and management of Hospitals, contributed by their authors for the use of the Johns Hopkins Hospital of Baltimore. These essays were written by Drs. JOHN S. BILLINGS of the U. S. Army, NORTON FOLSOM of Boston, JOSEPH JONES of New Orleans, CASPAR MORRIS of Philadelphia, and STEPHEN SMITH of New York. They were originally published in 1875. One volume, bound in cloth, price $5.

A pamphlet containing the addresses of FRANCIS T. KING, President of the Hospital, DANIEL C. GILMAN, President of the University, and JOHN S. BILLINGS, Medical Adviser to the Hospital Trustees, at the opening of the Hospital, May 7, 1889, may be obtained on application.

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PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

Dysentery—Abscess of Liver—Amœba Coli in Stools and Sputum—Death—Necropsy.—Dr. LAFLEUR.

This case is the fourth in a series of cases of dysentery complicated by abscess of the liver, in which the amœba coli was found during life in the stools and sputum of the patient, and in the various lesions at the autopsy.

George S., a marketman, aged 35, was admitted to the Johns Hopkins Hospital on January 12th, 1891, suffering from looseness of the bowels and cough with copious expectoration. With the exception of several attacks of chills and fever, the last of which occurred ten years ago, he had been in perfect health until the summer of 1890. At this time he had pains in his back, general lassitude, loss of appetite, and occasionally passed a little blood with his stools. He suffered no further inconvenience until the first week of September, when diarrhœa came on, which was severe for two weeks. He had no pain, but passed blood and mucus by the bowel, though not in large quantities. About the end of November, while still suffering from diarrhœa, he began to have severe pains in the abdomen, the right side of his chest and about his right shoulder blade. Coincidently with this he began to cough and to spit up a blood-stained viscid matter. Both the cough and the expectoration were paroxysmal, and his pain was increased when he lay on either side instead of on his back. During the three weeks previous to his admission to the hospital, his diarrhœa had increased in severity, and he had as many as fifteen movements in twenty-four hours, which he described as being dark colored, watery, but containing no blood. He had had no rigors and little fever, but occasionally had sweated profusely, and had lost flesh since the beginning of his illness. On his admission the patient was very weak, emaciated, pale and sallow. He lay quietly in bed without dyspnœa, and from time to time coughed up a viscid reddish-brown muco-pus. He had no fever, and his pulse was 120. Physical examination revealed the following points: General abdominal tenderness, without distention, more marked in the epigastrium and along the course of the colon. An extension both upwards and downwards of the limits of liver dulness in front, in the flank and behind. Tenderness on pressure, and slight bulging over the lower ribs on the right side, but no fluctuation. At the base of the right lung dulness and increased tactile fremitus, with distant tubular breathing and numerous râles. The dulness shaded off gradually upwards to normal resonance, a little below the spine of the scapula. Left lung normal throughout, and heart sounds normal. Blood count: red corp., 3,956,000; white corp., 53,000 per cub. mm. Sputum, muco-purulent, frothy, viscid, reddish-brown, with patches of a yellowish color. Under the microscope it contained pus cells, red blood corpuscles, large pigmented and fatty alveolar cells from the lung, elastic tissue fibres, granular detritus, and a number of actively moving amœbæ of various sizes, many containing red blood corpuscles. Stools frequent, watery, very offensive, containing brownish-red mucus, greenish shreddy material, and small whitish necrotic-looking masses. Actively moving amœbæ were numerous, particularly in the last named portions of the stools, and they were similar in all respects to those seen in the sputa.

From January 14th to January 24th there was irregular fever, with a weak pulse varying from 120–150. The movements were at first very frequent, but gradually diminished to three or four in the twenty-four hours, while on the other hand the cough became more troublesome, and the expectoration more abundant. Starch and laudanum injections were administered for six days, after which quinine injections were given in a strength of 1–5,000 twice daily, preceded by cocaine injections to diminish the irritability of the rectum. At night morphia was administered hypodermically. The patient gradually grew weaker, and died on the afternoon of January 24th.

The autopsy performed by Dr. Councilman may be summarized as follows: On opening the peritoneal sac a general peritonitis without perforation was found. The exudation was fibrinous and fibrino-purulent, thin and grayish. It was most abundant in the fissure of the liver, and between the liver and diaphragm. The peritoneum over the small intestine was thickened, juicy and slightly roughened. Adhesions were found only between the liver, stomach and colon, and these were quite recent. The liver extended 13 cm. below the ensiform cartilage. The right lung was firmly adherent to the posterior portion of the diaphragm and pleura. Anteriorly there was a small amount of exudation similar to that found in the peritoneal sac. The lower lobe of the right lung was consolidated, of a translucent grayish color and firm consistency, and in its lower portion there was an abscess cavity, with ragged necrotic walls, 7 × 6 cm., which communicated by a perforation in the diaphragm with the liver. The liver itself was much enlarged, and on its surface were numerous small abscesses. On the upper and posterior surface of the right lobe there was a large abscess with firm fibrous walls communicating with the abscess cavity in the lower lobe of the right lung, and in the centre of the right lobe was a still larger abscess, 8 cm. in diameter. There were in all about twenty abscesses, large and small. The smaller ones contained a whitish-gray, spongy, necrotic-looking material, with a thin fluid in its interstices, the larger ones a more diffluent, grayish-green, somewhat stringy mass. Only the abscess communicating with the lung had a well-defined capsule. The large intestine was ulcerated throughout, the ulcerations being most extensive and destructive in the cæcum and ascending colon where only small islands of mucous membrane were left. The ileum also was ulcerated to a distance of 12 cm. above the valve. The other viscera were normal.

Microscopic examination of the peritoneal exudate, and of the material from the lung and liver abscesses, and from the bases of the intestinal ulcerations showed numerous, still actively moving amœbæ, similar to those observed during life in the stools and sputa.

The case is interesting, not only as an individual one, but as illustrating a type of a series of cases which forms, I think, a very definite clinical and anatomical picture. Dr. Councilman will discuss the pathological anatomy in detail; I wish merely to draw attention to the clinical aspect of these cases. It is a protracted and wasting disease, beginning usually with a painless diarrhœa without or with only slight febrile disturbance, and accompanied by loss of appetite, lassitude and slight emaciation. The stools are at first simply watery and contain little mucus or blood, but from the first the amœba coli is found in greater or less numbers. In more acute cases there may be a good deal of blood and mucus, and in such cases, more or less, abdominal pain and tenesmus is present. If the case is to terminate favorably these symptoms gradually disappear, though there may be slight exacerbations which delay convalescence, and finally the amœbæ disappear entirely from the stools. They may, however, be present for some time after the patient is passing fully formed faeces. If on the other hand the disease progress unfavorably there is an increase in the diarrhœa and abdominal symptoms, and a progressive emaciation and loss of strength. It is remarkable, however, that even in eventually fatal cases there are marked intermissions in the diarrhœa.

In a certain number of cases, after the disease has lasted from six to twelve weeks, there is evidence of involvement of the liver and subsequently of the right lung. This is indicated by pain in the epigastrium or right hypochondrium, or over the lower ribs on the right side, sometimes extending to the back. Fever of an irregularly intermittent type makes its appearance, sometimes with rigors and usually with profuse sweating. If the lung be involved there is at first a distressing hacking ineffectual cough, which is soon accompanied by expectoration of a reddish-yellow or reddish-brown viscid muco-pus. This is not unfrequently discharged suddenly in large quantities. There is not usually evidence of much enlargement of the liver, and in no case have we detected fluctuation at any time over the area of liver dulness. The physical signs of the involvement of the lower lobe of the right lung are at first always obscure and indefinite, and may remain so even after the patient has been spitting pus for weeks. This appears to be due to the fact that the abscesses, both in the liver and in the lung, are deeply situated towards the centre of the diaphragm, and are consequently not readily amenable to the usual methods of diagnosis. Even repeated exploratory punctures with a long and large-sized aspirating needle are often negative, owing to the viscidity of the abscess contents. When in addition to these more or less definite physical signs, there is added the continued presence of amœbæ in the stools and their appearance in the sputa, the clinical picture is complete. The prognosis is always uncertain, for even cases which are mild at first may progress gradually to

a fatal termination. When there is abscess of the liver and lung the outlook is extremely bad, even if the abscess be localized and amenable to surgical treatment. Three out of four cases of dysentery with abscess of the liver and lung have died, and the fourth case is still under treatment. In two of the fatal cases the abscesses were opened and drained, but the patients died some weeks after of exhaustion. For the diarrhœa large rectal injections of a solution of quinine of a strength of 1–5,000 have lately been used, and in some of the uncomplicated cases appear to have been of marked benefit.

Dr. BLACHSTEIN inquired if any definite mode of infection had been proven in these cases.

Dr. LAFLEUR said:—It is not possible to say anything definite about the source of infection. The fact that three of the cases of dysentery admitted to the hospital had been working on the same pier at the harbor, and had been accustomed to drink from a well near by suggested the possibility of this being the source of infection, but an examination of some of this water was negative as regards amœbæ.

In the present case the man drank usually the water supplied by the city, but on several occasions during the summer he had drunk water from a spring which was at times contaminated after rains with surface water coming from the "Spring Gardens," a low-lying tract of land in South Baltimore.

Dr. COUNCILMAN said:—The lesions in this case were interesting from the evident acuteness of the process. In the intestine there was not such a degree of undermining of the mucous membrane as was found in the other cases. Most of the lesions were large flat ulcerations, which were most prominent in the cæcum. In the ascending transverse colon there were smaller ulcers with the characteristic undermining of the edge and infiltration of the submucous coat. Ulcers similar to those in the colon were found in the lower part of the ileum. In none of the other cases was there any affection of the small intestine. The amœbæ were found in great numbers in these ulcers. They were in general most numerous in the small and most recent ulcers. Here they were found in the lymphatics and lymph spaces of the submucosa, and frequently they seemed to pass from this into the mucous membrane at a distance from the point of ulceration. They were also found in the muscular coat. Great numbers were found in the fat of the meso-colon where a large ulcer had penetrated through the intestinal coats into this tissue. The liver abscesses were interesting. In the contents of all of these numerous actively moving amœbæ were found when the autopsy was made. The abscesses contained a thin gelatinous looking liquid and masses of firmer material. In the fresh examination very few pus cells were found in this fluid. In sections which were made through an entire abscess the greater part of the contents was made up of a granular-looking material in which there were numerous amœbæ. In this material there were small islands of liver tissue remaining. In other parts of the liver there was found everywhere a necrosis with hyaline degeneration of the liver cells around the central veins. In the abscess in the lung numerous amœbæ were found both in the fresh and hardened tissues. An interstitial pneumonia in the lung around the abscess was present.

In this case there seemed to be two well-marked sets of lesions. First, those in which the lesions were distinctly focal in character marked by abscesses and ulcerations which were due to the direct action of the amœbæ on the tissues, and in which the amœbæ were found. Second, lesions of a more diffuse character marked by necroses and hyaline degeneration of the cells and which were due to the action of a chemical substance produced by the amœbæ. The change in the liver around the central veins of the lobules were of this nature as was also a hyaline degeneration of the upper layers of the intestinal muscular coat.

Acute Miliary Tuberculosis.—DR. COUNCILMAN.

Dr. Councilman exhibited specimens from a case of acute general miliary tuberculosis. The specimens were from a boy, 6 years old, who was under the care of Dr. Booker to whom we are indebted for the autopsy. The lesions are interesting both in their extent and in the ease with which the entry of the tubercle bacilli into the general circulation can be traced. Both lungs are filled with very fine tubercles and there are several caseous foci in branches of the pulmonary veins. The largest of these is in a branch, ½ cm. in diameter, in the upper lobe of the right lung. The wall of the vein over a space 1½ × ½ cm. is covered with a caseous necrotic mass which is rough and irregular on the surface. From this, the tubercle bacilli could enter the general circulation and produce the miliary tubercles found in all the organs. The tubercles in the kidneys were interesting from their distribution. In both there were fine disseminated tubercles, but in the right kidney there were in addition, distinct tuberculous infarctions. Two triangular areas corresponding to the distribution of large branches of the renal artery were entirely filled with tubercles. These had probably resulted from the plugging up of these branches with small masses of the tuberculous material from the lung veins, while the disseminated tubercles were probably due to the lodgment of single bacilli.

DR. BOOKER:—The subject of the specimens Dr. Councilman has just exhibited, was a colored boy, 6 years old. He was brought to the dispensary of the Woman's Medical College, January 20, 1891, suffering with fever, weakness, difficult breathing, loss of appetite and irregular bowels.

He was apparently healthy and well nourished up to two months ago, when he commenced losing flesh and having shortness of breath, drowsiness and no inclination to play. The last two weeks he had fever and constipation alternating with diarrhœa, but he was not considered seriously sick more than one week.

His mother is stout and healthy; she has had 7 children and one miscarriage. The remaining six children are healthy. Father is delicate looking and two of his sisters died of consumption.

This child had pneumonia in infancy; at 2½ years he had swelling of the scrotum which was thought to be scrofulous by the attending physician. At 3 years of age he had measles, and since then he has had a discharge from both ears.

Condition when first seen at the dispensary: Very tall for his age; emaciated; had a painful expression of the face and looked sick. Respiration 70 and labored; pulse 160; temperature 100.4°. Dulness with tubular breathing over the apex of the right lung; fairly good percussion resonance and harsh breathing over the rest of the chest. No râles were heard at this time. The heart appeared healthy. Abdomen was soft.

The child was placed in the Good Samaritan Hospital, and under observation 8 days. His respiration continued very rapid, from 80 to 100. There was no constancy in the physical signs of the chest. At some examinations all kinds of râles were heard, at other times very few, if any, râles were heard. The dulness and tubular breathing were not always present, and at times it was astonishing to find the small amount of abnormal sounds in the chest in connection with the rapid and labored breathing. There was no cough at any time of the sickness. The temperature was irregular, from 101° to 103.2° and often reached the highest point in the morning.

The child frequently had loud, sharp cries of pain.

In addition to the condition Dr. Councilman has described, there was a small tubercular nodule on the outer surface of the bladder and one, the size of a grain of wheat, in the left epididymis. The testicles appeared healthy. The pleura was strongly adherent all round the chest, and the lungs were removed with considerable difficulty.

Meeting of March 2nd, 1891.

Dr. OSLER in the chair. 37 members present.

Two Cases of Leukaemia.—Dr. TOULMIN.

While leukaemia can no longer be considered a rare disease, the fact that Birch-Hirschfeld, in 1883, was able to collect only 200 cases reported in literature up to that time,[1] shows that it is not common. We are therefore to be considered fortunate in having met with a second case so soon.

It is more, however, on account of the new interest that has been given to the disease through the researches of Ehrlich and his students, that this second case is reported, and further notes made in the first.[2]

The history of Case II is as follows:—

Annie H., colored, married, aet. 30, washerwoman, applied at the dispensary, February 25, 1891, and was sent to the gynecological department, as she thought she had "womb trouble." Nothing abnormal was found in

[1] Osler: Pepper's System of Medicine, 1885.

[2] Bulletin of the Johns Hopkins Hospital, January, 1891.

the genito-urinary apparatus except a relaxed outlet; but a large mass was discovered in the left abdominal region, evidently not pelvic in origin, and for this reason she was transferred to the medical side the next day. She then complained of being weak, of having a pain in her left side, and a swelling in the "stomach."

She knew nothing of her grand-parents. Her mother had died when she was young, cause unknown. Father and two sisters are well; had no brothers. Husband is well,—has not lived with her for two years. Married at 17. First child died when four months old, second when one and one-fourth years; third was a miscarriage at three months;—not pregnant since.

Patient has been remarkably free from disease. Had typhoid when a child, and is subject to slight sore throats, knows of no other illnesses. Very well when young, never had malaria; denies specific disease. Began menstruating at sixteen, and has always been regular, even up to the present time.

The present illness began early in last November, with severe cough and expectoration, shortness of breath and failing strength. She began to lose flesh about Christmas, and has fallen in weight from 170 to 120 lbs. She also noticed at this time that she had not as much color as formerly. Pain first appeared in January, chiefly along the left costal margin, but the swelling in the abdomen was first observed only four weeks ago. Both she and the doctor called in at that time, think it has become larger. She had slight oedema of the feet for a few days last week. She has had some palpitation of the heart, but no shortness of breath, has had no cough for a week. There have been no hemorrhages. The bowels have been obstinately constipated. Her food does not seem to digest well; appetite poor. Is often dizzy. Sight unaffected. She has noticed nothing wrong with her water. Is too weak to work.

Examination. Well built, fairly well nourished woman. Face pale; mucous membranes very anaemic; slight throbbing in vessels of neck; no capillary pulse. No oedema. Eyeballs quite prominent; pupils normal. Pulse 120, fair volume, not weak. Temperature 99.5° F.

Lungs are clear throughout.

Heart. Apex beat in 5th interspace within nipple line. Sounds are clear and loud; no murmur at base. Venous hum in vessels of neck not detected.

Liver. Dulness from 6th interspace to costal margin, in nipple line. Edge just palpable.

Abdomen. The left side is rather more prominent than the right; especially in the lower epigastric, the umbilical, and upper hypogastric regions. The edge of a tumor-mass occupying this region is distinctly seen in the median line, notched just above the umbilicus; and it is so clearly defined through the thin abdominal wall, that one is almost sure in saying, from inspection alone, that the mass is an enlarged spleen.

Palpation. The tumor mass is very hard, firm, smooth, slightly tender and freely movable. There is no pulsation. The edge is freely palpable everywhere below the costal margin, but more especially along the right border, just beyond the median line. The notch is remarkably well defined. The lowest border is felt in the median line, 6.5 cm. from the pubes, and 7 cm. from the umbilicus. The right side of the abdomen is soft and pliant. There is no ascites.

Percussion. There is a normal tympanitic note over the right side of the abdomen, the lower fifth of the left and along the extreme left side. There is vertical dulness from the 7th int. sp., mid. axillary line, to the costal margin; from the 6th int. sp., nipple line for a distance of 22 cm.; from the tip of the ensiform to 6.5 cm. above the pubes, a distance of 24 cm. The extreme right edge is 2.5 cm. to the right of the median line, at a point 7 cm. above the umbilicus; at the umbilicus it is 1.5 cm. to the right. The left border slopes gradually from the lowest point in the median line to the mid. axillary line, where it passes beneath the ribs, and is 1 cm. to the right of the ant. sup. iliac spine. The notch is 2.5 cm. above the umbilicus, and extends 1.5 cm. to the left of the median line.

Greatest horizontal diameter of spleen, 2.6 cm., in a line 7 cm. above umbilicus; greatest oblique diameter, from 7th int. sp., mid. axillary line, to median line 6.5 cm. from pubic bone, 35 cm. Abdomen at umbilicus measures 74.5 cm.; and 74 cm. at a point 7 cm. above umbilicus.

Urine. Light yellow, acid, mucous sediment, sp. gr., 1.017. No albumen, no casts, a few mucous cylindroids.

Eyes. Left eye normal; hemorrhagic retinitis in right eye.

Blood. R. 3,016,000; W. 163,000; Ratio, W : R :: 1 : 18.5.

Haemoglobin 41 per cent. See below.

Treatment. Arsenic was immediately commenced. Three drops of Fowler's Solution, three times a day, to be increased by one drop every three days.

Considering the good general condition of the patient, the moderate enlargement of the spleen, and the fact that there have been no hemorrhages and no diarrhœa, the outlook is not unfavorable.

It is of some interest that both our patients are colored.

CASE I.[1]—The boy continued improving until the first of December, when he went to his home in Virginia, and for nearly eight weeks was without treatment. He grew steadily worse, and returned to the city late in January, applying at the dispensary, January 29. His abdomen had swollen considerably; the oedema was worse than ever; his face was thin and drawn. He was quite short of breath, could not see at all well; had no appetite and felt very weak. For some days he had had fever in the afternoon. There had been no diarrhœa, but rather a tendency to constipation. There had been nose bleeding on one occasion, no other hemorrhage.

The note made on the 29th was as follows:—Patient looks much worse than when last seen. Color is still good. Tongue furred. Marked pulsation in vessels of neck. No capillary pulse. Pulse 96. Temperature 100° F. Respirations 40. Legs oedematous to the hips; genitalia not involved.

Heart. Apex beat in 5th int. sp., diffused pulsation in 3rd left int. sp. Cardiac dulness at 3rd int. sp., mid. sternum and nipple line. At apex 1st sound accompanied by a rumbling. Faint systolic murmur at base.

Lungs. Clear throughout.

Liver. Dulness at 6th rib, nipple line, impossible to make out lower limit.

Abdomen. Looks decidedly larger. It is more symmetrically distended, left side being less prominent than before. At umbilicus it measures 94.5 cm., and 9 cm. above this the circumference is greatest, 99.5 cm. The spleen has the same characteristics to the touch as when first noted. It is slightly tender at the upper margin.

The lower edge is felt 2 cm. above the middle of Poupart's ligament on the right side, 5 cm. from the right ant. sup. spine of the ilium, and 4 cm. from the pubes. To the left the edge is felt resting on the iliac crest.

Percussion. There is dulness in extreme right flank; intestinal tympany in right hypochondrium and umbilical regions. Splenic dulness extends from 8th rib, mid. axillary line, obliquely towards middle of Poupart's ligament, a distance of 48.5 cm. The extreme right edge at the level of the umbilicus is 10 cm. to the right of the median line; to the left, the extreme edge is distant from the median line 34.5 cm., at the level of greatest circumference.

There is no pulsation and no murmur. Involvement of bones and glands not to be detected. The blood condition will be found below.

Fowler's solution was begun, ten and twelve minims three times a day, so that by the 25th of February he had taken nearly an ounce and a half. Except for a bad cough, the result of a heavy cold, and extensive oedema now involving the genitals, he felt well. He was stronger, had a good appetite, not short of breath, color good, sight much better. The abdomen looked decidedly smaller, was soft, spleen undoubtedly smaller. Dulness began at the 8th rib, mid. axillary line, and extended to within 12 cm. of the right superior spine of the ilium, and on a level with it, a distance of 43 cm. The lower edge was 7 cm. from the pubes, the extreme right edge 3 cm. to the right of the umbilicus.

The abdomen at the umbilicus measured 95 cm. and 99 cm. at a point 12 cm. above the umbilicus.

Of still greater interest is the blood condition, which shows most marked improvement.

The question arises: To what extent is the improvement the result of treatment? It seems improbable that such marked benefit should be independent of treatment, as has been observed in other cases.[2] The improvement, nevertheless, is likely to be quite temporary.

Urine. March 2nd. Reddish yellow, acid, no albumen, sp. gr. 1,014, mic. exam., amorphous urates.

The following Table shows the variations in the measurements.

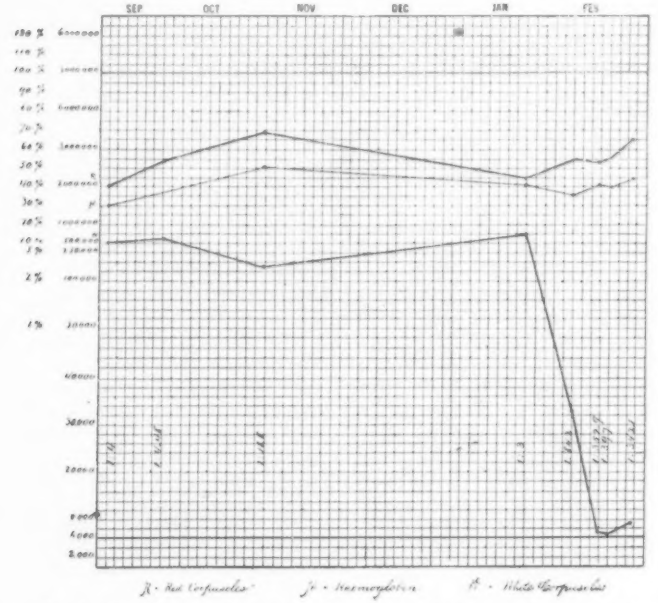
[1] Bulletin of the Johns Hopkins Hospital, January, 1891, p. 17.

[2] Osler, *Ibid.*

	Sep. 15, '90.	Jan. 29, '91.	Feb. 25, '91.
Circumference of abd. at umbilicus,	91.5 cm.	94.5 cm.	95 cm.
Greatest circumference,	91.5 "	99.5 "	99. "
Upper limit, splenic dulness,	7th rib.	8th rib.	8th rib.
Lower limit of same, from pubic bone,	7. cm.	4. cm.	7. cm.
Greatest oblique diameter,	41. "	48.5 "	43. "
Extreme right edge, from median line,	9. "	10. "	3. "

Dr. THAYER said:—Dr. Toulmin has kindly given me this chance to say a few words with regard to the condition of the blood in this patient which he has offered me every opportunity of examining. Since I first saw the patient, on November 2d, I have on various occasions made careful counts of the blood corpuscles, estimated the percentage of haemoglobin, and studied the formed elements on cover glass specimens prepared and stained according to the methods of Ehrlich.[1]

The estimates of the number of the corpuscles were carefully made. In each case one whole field of the Thoma-Zeiss blood counter was first counted, and then at least three more fields were counted for the white alone. In this way, I believe, a fair estimate may be obtained of the number of white corpuscles. One is also able to control the original count of the red, for if, on examination of the second slide, any material difference in the number



of red corpuscles is noted, a second or even a third count can be made. Where the proportion rises as high as 1 : 3, as on January 29th, two, three or four whole fields were counted for both white and red.

The accompanying chart shows the variations in the number of the red and white corpuscles and in the percentage of haemoglobin since the first visit of the patient to the dispensary.

The first two estimates are not mine.

The first estimate, that of September 17th, showed: R. 2,008,000. Proportion of white to red 1 : 4. Haemoglobin 30 per cent.

On October 2nd, after taking arsenic, the estimate was: R. 2,700,000. Proportion of white to red 1 : 4.48.

November 2nd (my first examination), R. 3,430,000. Proportion of white to red 1 : 18.8. Haemoglobin 51 per cent.

From this time to January 29th, 1891, the patient was not seen, and, as Dr. Toulmin has stated, had discontinued treatment. On this date the estimate was: R. 2,171,000, W. 714,000. Proportion of white to red 1 : 3. Haemoglobin 41 per cent. (The great number of white corpuscles gave the diluted blood so cloudy a color, that the reliability of this estimate, though carefully made, is, I think, doubtful.)

February 14th. Patient has been taking Arsenic in increasing doses. R. 2,779,333, W. 33,000. 1 : 84.2. Haemoglobin 35 per cent.

February 21st. R. 2,647,333, W. 7,500. 1 : 352.9. Haemoglobin 41 per cent.

Thus in 19 days the number of leucocytes in a cubic millimeter fell from 714,000 to 7,500, an hundred fold diminution.

February 25th. R. 2,779,333, W. 7,000. 1 : 397. Haemoglobin 39 per cent. (On March 5th, the estimate was R. 3,250,000, W. 9,500. 1 : 342.1. Haemoglobin 44 per cent.)

Thus, in less than three weeks after return to treatment, the excess in leucocytes entirely disappeared. And this condition has persisted, so that to-day the mere numerical estimate of the blood would give us no hint that a leukaemic condition had ever existed.

I have also studied the elements of the blood with some care according to Ehrlich's methods of differential staining. Before describing the results, let me say a few words with regard to the methods and the elements which one sees in normal blood.

In 1879-80, Ehrlich first announced the result of careful researches he had made in the "color-analysis," as he called it, of the elements of the blood. He made use of dried cover-glass specimens according to the methods of Koch, which were carefully prepared so as to have as thin a film of blood as possible, and were "fixed" by heating for from one to two hours on a copper bar at a point between 100° and 120° C.

By studying the effect of various coloring matters, he discovered that the protoplasm of certain of the leucocytes contained granules which had affinities for certain distinct classes of coloring matters, and that by the use of these coloring matters cells which might otherwise be indistinguishable from one another could be differentiated.

In view of these properties, brought out by the "color-analysis," and of the fact that he never found but one variety of granulation in a single cell, he proposed the term "specific granulations of the blood."

The coloring matters Ehrlich divides into two great groups, (1) the acid, and (2) the basic.

An acid coloring matter is one in which the staining principle is the acid part of the salt. The reaction of the solution of the salt, or the fact that the salt is or is not chemically acid has nothing to do with the case. An example is picrate of ammonium; this is an acid coloring matter because the picric acid is the staining principle. A basic coloring matter, on the other hand, is one where the staining principle is the base. Now Ehrlich has discovered in all, seven different varieties of granulations in the blood of various different animals, but of these, only three come into consideration in the study of human blood, and only two, indeed, have as yet been shown to be of practical diagnostic value.

(1) In the first place, there are found in human blood, cells with relatively large, ovoid or round, yellowish, highly refractive, fat-like granules, which have an affinity for acid coloring matters, and are stained by these alone and by all of this group. The chemical nature of these granules is doubtful; they have been proven to be neither fat nor haemoglobin as has often been thought, and Ehrlich considers them to be of an albuminoid nature and a specific product of the cell protoplasm. These granules have been called *Eosinophilic* because of their affinity for eosin.

(2) Under certain conditions one finds in human blood a granulation which stains only in basic coloring matters. This *basophilic granulation* has not as yet any great importance from a diagnostic point of view. It seems to be identical with the granulation of the "mastzellen" which appear in the tissues, and the name has been applied to these basophilic cells in the blood.

(3) The most common granulation in the blood is one which is stained by neither acid nor basic coloring matters alone, but which takes on a stain when a fluid is used containing examples of both, as a result of a combination of the two. This is the so-called "Neutrophilic" granulation; it occurs in the majority of leucocytes.

In normal blood one finds the following varieties of the colorless elements:

(a) Lymphocytes. Small cells about the size of red corpuscles, somewhat larger or smaller, with a large, round, deeply staining nucleus, surrounded by a narrow rim of non-granular protoplasm. These cells seem to be derived in main part from the lymphatic apparatus—hence the name.

[1] *Ehrlich*, Verhandl. der Berliner Physiolog. Gessel., May 15th, 1879, January 17th, 1879; Zeitschrift für Klin. Med., I, 1880; Berlin. Klin. Woch., 1880, No. 28; Berlin. Klin. Woch., 1881, No. 3; Deutsch Med. Woch., 1883, No. 46; Charite Annalen, XII jahrg. *Westphal*, Diss., Berlin, 1880. *Schwarze*, Diss., Berlin, 1880. *Spilling*, Diss., Berlin, 1880. *Einhorn*, Diss., Berlin, 1884. *Uthemann*, Diss., Berlin, 1887. *Gollasch*, in Friedländer-Eberth's "Mikroscopische Technik." *Gabritchewsky*, Archiv. für Experiment. Path. u. Pharm., 1890, 28, 1 and 2.

(*b*) Large mononuclear leucocytes. Large cells, several times as large as the red corpuscles, with a large oval or elliptical nucleus, and relatively considerably more protoplasm, which is also ungranulated.

(*c*) Transition forms. Cells which resemble the last mentioned variety except that there are indentations or irregularities in the nuclei indicating that these are beginning to be polymorphous.

These seem to be simply transition forms between the large mononuclear leucocytes and

(*d*) Polynuclear leucocytes ("neutrophiles.") These are of about the same size or somewhat smaller than the last variety. The nucleus consists of a long intensely staining body, which is bent and twisted on itself into most bizarre and irregular shapes. Often the nucleus seems to be broken and the cell seems to have two or three nuclei; it is however probable, as Ehrlich himself says, that the nucleus is, during life, only polymorphous, and that the polynuclear appearance is due to the preparation. The protoplasm of these cells is thickly filled with a very fine neutrophilic granulation.

(*e*) Eosinophiles. Cells of about the same size as the last variety with a single round, ovoid, or polymorphous nucleus and containing large round or ovoid eosinophilic granules.

In normal blood these varieties occur in a quite constant and definite proportion one to another, as follows: lymphocytes, 20–30 per cent.; polynuclear, 60–75 per cent.; mononuclear and transition forms, 6 per cent.; eosinophiles, 2–4 per cent.

The lymphocytes, as has been said, seem to come from the lymphatic apparatus while the large mononuclear and polynuclear forms seem to come from the spleen and bone marrow. The eosinophiles seem to arise solely in the bone marrow.

Under certain pathological conditions these proportions vary, and the changes which occur in the common form of leukaemia, the splenic or more properly the splenic-myelogenous leukaemia, are characteristic. In this form of leukaemia, we see the greatest increase in white corpuscles which occurs under any conditions; the proportion of white to red may be as 1 : 1. And, as we might expect, the cells which take part in this increase, are mainly those which seem to be derived from the spleen and bone marrow. The lymphocytes take little or no part in this increase, and are, therefore, present in a greatly reduced relative proportion. Eosinophiles are present in a normal, or commonly increased relative proportion, and thus, of course, in a greatly increased total number. Their presence in nearly every field under the microscope, often in large numbers, is a striking picture, and characteristic of this disease. The proportion of the large mononuclear and transition forms presents about the normal variations.

Polynuclear neutrophiles are present in normal, increased, or, more often, in diminished relative proportion.

The most characteristic feature of the blood is, however, the appearance of a form of cell which does not appear in the normal blood of adults.

This is a cell as large, or larger than the large mononuclear variety in normal blood, and similar to this morphologically, except that the protoplasm is filled with fine neutrophilic granules. These forms would seem, possibly, to represent an arrest or perversion of development. The nucleus of the ordinary mononuclear leucocyte does not become polymorphous, and the neutrophilic granules, which usually appear coincidently with this change, are developed, while the cell may acquire a larger size than any other element which occurs in the blood.

These elements seem never to acquire the power of amoeboid movement which the polynuclear cells possess. They appear to arise in the marrow and have been called by Ehrlich "myelocytes."

Varying numbers of "mastzellen" also appear in this form of leukaemia; also a certain number of polynuclear cells which, with mixtures staining the neutrophilic and eosinophilic granules, (the Ehrlich-Biondi triple stain) show no granulation.

The red corpuscles may show a greater or less poikilocytosis, and nucleated red corpuscles are present, often in considerable numbers.

The characteristic features then, in the blood of this form of leukaemia, are (1) The enormous increase in colorless elements. (2) The increased number of eosinophiles. (3) The presence of myelocytes. (4) The presence of nucleated red corpuscles.

This picture is characteristic, and a marked contrast to that in all other considerable leucocytoses, where the increase takes place solely in the polynuclear neutrophiles; with a relative diminution in all other forms. Acute lymphatic leukaemia is the only exception; here the increase occurs solely in the lymphocytes.

The blood in this case has been typical of splenic-myelogenous leukaemia. Specimens have been examined with various different staining solutions—*i. e.*, methylene blue; methyl green; dahlia; eosin and methylene blue; eosin, migrosin and aurantin; and Ehrlich's triple stain of methyl green, ac. fuchsin, and orange G.

In the first specimens recorded, those of Nov. 9, 1890, there was a slight poikilocytosis, and a moderate number of nucleated red corpuscles, chiefly of small size, with intensely staining, round, somewhat refractive nuclei ("normoblasts," Ehrlich). Lymphocytes were present in greatly reduced relative proportion, while eosinophiles were numerous, and there was a considerable number of myelocytes. Mastzellen were also present in certain proportion, as were also polynuclear cells which, with the triple stain, showed no granulation.

The so-called "degenerative forms" of red corpuscles, *i. e.*, those taking up basic coloring matters to a certain extent, were present. This characteristic was also noticed in the bodies of most of the nucleated red corpuscles.

The accompanying chart shows the percentage of the different varieties of leucocytes on different dates. These estimates are based on differential counts of at least 1,000 leucocytes in each case.

	Normal Blood.	Nov. 9, 1890.	Jan. 23, 1891.	Feb. 7, 1891.	Feb. 14, 1891.	Feb. 21, 1891.	Feb. 25, 1891.
Lymphocytes,	20–30%	2.1%	0.96%	1.5%	2.7%	6.9%	10%
Polynuclear,	60–75%	73.8%	70.%	83.9%	84.7%	83.2%	78.1%
Mononuclear and Transition.	6.0%	4.6%	3.%	1.5%	2.1%	2.5%	2.3%
Eosinophiles,	2–4%	4.8%	2.3%	4.2%	1.6%	3.%	4.4%
Myelocytes,	0%	14.7%	23.5%	8.6%	8.5%	4.%	4.7%

Thus it will be seen that on his return to Baltimore, after giving up treatment, the percentage of lymphocytes was under 1 per cent. while that of the myelocytes had increased at the expense of the polynuclear forms.

In this specimen the nucleated red were numerous. Many were much larger than the ordinary red corpuscles, and certain of these contained large round weakly staining nuclei ("megaloblasts," Ehrlich). Many of the nucleated red corpuscles showed dividing nuclei, and in one instance the whole corpuscle was found to have assumed an hour-glass shape with a half of the divided nucleus at each pole. Poikilocytosis was more marked.

With the sudden drop in the total number of white elements, the immediate diminution in the proportion of myelocytes and the increase in the percentage of the lymphocytes and polynuclear varieties will be noticed.

In the latter specimens examined the poikilocytosis was very marked and striking. "Degenerative forms" were very numerous as were nucleated red corpuscles. A considerable number of these latter were megaloblasts. A large number of the nucleated red corpuscles showed signs of nuclear division, and several bodies were found showing an hour glass constriction as above described; one, where the division had already taken place save for a fine filament which still connected the two daughter cells.

The specimens under the microscopes are stained with the triple stain of methyl green, acid fuchsin, and orange G. The nuclei are stained green, those of the nucleated red corpuscles nearly black; the red corpuscles orange; the eosinophilic granules red; the neutrophilic granules a violet or lilac color.

This case is remarkable in many respects from a haematological point of view. I am not aware that any other case of undoubted leukaemia has been reported where the excess in white corpuscles has fallen in so striking and critical a manner.

Just such a case as this demonstrates the value of these methods of study which we owe to Ehrlich. Though the physical examination of the patient at the present time might suggest most strongly, a leukaemia, the mere numerical estimate or, indeed, the examination of the fresh blood might give us no hint that such a process had ever existed.

The presence, however, of an appreciable percentage of typical myelocytes, as revealed by these methods of contrast staining, might put us upon the proper clue, and lead us to anticipate or recognize the possibility of a future return of the leukaemia.

The examination of cover-glass specimens from case II shows the blood to be typical of splenic-myelogenous leukaemia.

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